UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

CERTIFICATION OF ADAM M. SLATER IN SUPPORT OF PLAINTIFFS' *DAUBERT* MOTION TO EXCLUDE TESTIMONY OF JANICE K. BRITT, PH.D.

ADAM M. SLATER, hereby certify as follows:

1. I am an attorney at law within the State of New Jersey and a partner with the law firm of Mazie Slater Katz & Freeman, LLC, and serve as Plaintiffs' Co-Lead Counsel. I am fully familiar with the facts and circumstances of these actions. I make this Certification in support of Plaintiffs' motion to exclude the testimony of Janice K. Britt, Ph.D.

2. Attached hereto as **Exhibit A** is a true and accurate copy of The Center for Public Integrity, *How Industry Scientists Stalled Action on Carcinogen* (May 19, 2014), https://tinyurl.com/zyp3zn5j.

3. Attached hereto as **Exhibit B** is a true and accurate copy of Natural Resources Defense Council, Comments from NRDC on EPA's TSCA Systematic Review (Aug. 16, 2018), https://tinyurl.com/att66nas.

4. Attached hereto as **Exhibit C** is a true and accurate copy of The Roanoke Times, *FERC study finds no risk from protective coating of Mountain Valley Pipelin*e (Oct. 8, 2020), https://tinyurl.com/czeps68v.

5. Attached hereto as **Exhibit D** is a true and accurate copy of Expert Report of Janice K. Britt, Ph.D.

6. Attached hereto as **Exhibit E** is a true and accurate copy of the September 23, 2021 Deposition Transcript of Janice K. Britt.

7. Attached hereto as **Exhibit F** is a true and accurate copy of Roberts, Jordan, Warren, Britt, & James, *Evaluation of the carcinogenicity of 1,1-dichloroethylene (vinylidene chloride)*, REGUL. TOXICOL. PHARMACOL. 35, 44-55 (Feb. 2002).

8. Attached hereto as **Exhibit G** is a true and accurate copy of an excerpt of Williams, James, & Roberts, *Principles of Toxicology: Environmental and Industrial Applications* (John Wiley & Sons, Inc. 2000).

9. Attached hereto as **Exhibit H** is a true and accurate copy of James, Britt, Halmes, & Guzelian, *Comments on recent discussions providing differing causation methodologies*, HUM. EXP. TOXICOL. 33, 110 (Jan. 2014).

10. Attached hereto as **Exhibit I** is a true and accurate copy of Pottegård, Kristensen, Ernst, Johansen, Quartarolo, & Hallas, *Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study*, B.M.J. 12, 362 (Sept. 2018).

11. Attached hereto as **Exhibit J** is a true and accurate copy of Gomm, Röthlein, Schüssel, Brückner, Schröder, Heß, Frötschl, Broich, & Haenisch, *N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer: A Longitudinal Cohort Study Based on German Health Insurance Data*, DEUTSCHES AERZTEBLATT INTERNATIONAL 118, 357-62 (2021).

12. Attached hereto as **Exhibit K** is a true and accurate copy of Rudén & Hansson, *Evidence-based toxicology: "sound science" in new disguise*, INT. J. OCCUP. ENVIRON. HEALTH 14, 299 (Oct. 2008).

13. Attached hereto as **Exhibit L** is a true and accurate copy of James, Britt, Halmes, and Guzelian, *Evidence-based causation in toxicology: A 10-year retrospective*, HUM. EXP. TOXICOL. 34, 1250 (Dec. 2015)

14. Attached hereto as **Exhibit M** is a true and accurate copy of *The Role of Systematic Review in the Practice of Toxicology and Risk Assessment – An Appreciation for* ***the Primary Tool in Evidence-Based Practice***, TOXICOLOGY: OPEN ACCESS 2, 1 (2016).

15. Attached hereto as **Exhibit N** is a true and accurate copy of *Kirk v. Schaeffler Group USA, Inc.*, No. 3:13-cv-5032-DGK, 2015 WL 12426834 (W.D. Mo. Sept. 29, 2015).

16. Attached hereto as **Exhibit O** is a true and accurate copy of *Player v. Motiva Enterprises LLC*, No. Civ. 02–3216(RBK), 2006 WL 166452 (D.N.J. Jan. 20, 2006).

17. Attached hereto as **Exhibit P** is a true and accurate copy of FDA, *FDA presents interim limits of nitrosamines in currently marketed ARBs* (Dec. 19, 2018), https://tinyurl.com/4rkpdf5h.

18. Attached hereto as **Exhibit Q** is a true and accurate copy of EPA, *N-Nitrosodimethylamine*, https://tinyurl.com/9krh69u9.

19. Attached hereto as **Exhibit R** is a true and accurate copy of EPA, *N-Nitrosodiethylamine*, https://tinyurl.com/48y7nejw.

20. Attached hereto as **Exhibit S** is a true and accurate copy of an excerpt from the USP, Summary, Highlights and Timeline of General Chapter <1469> Nitrosamine Impurities (July 20, 2018).

21. Attached hereto as **Exhibit T** is a true and accurate copy of SOLCO00024226, ZHP 129.

MAZIE SLATER KATZ & FREEMAN, LLC
Attorneys for Plaintiffs

By: /s/ Adam M. Slater

Dated: November 1, 2021

Exhibit A

EXHIBIT
Britt-8

TOXIC CLOUT

Published — March 13, 2013
Updated — May 19, 2014 at 12:19 pm ET

HOW INDUSTRY SCIENTISTS STALLED ACTION ON CARCINOGEN

For the past 60 years, water polluted with chromium (VI) has plagued Hinkley, Calif., the desert town made famous by the film "Erin Brockovich." Although residents there won their lawsuit against the polluter, Pacific Gas & Electric Co., there's still a debate over whether the compound causes cancer in drinking water. The Environmental Protection Agency says yes, but industry scientists disagree.
Miles O'Brien, PBS NewsHour

David Heath

HINKLEY, Calif. – Ten days before Christmas 1965, Pacific Gas & Electric Co. station chief Richard Jacobs walked a half-block on a dusty road lined with scraggly creosote shrubs to check out a neighbor's toilet.

Jacobs carried with him a secret, something he referred to as the "chromate problem."

Starting in 1952, the power company began mixing a toxic form of chromium with water to prevent rust at a new pipeline pumping station in Hinkley, a remote desert community united by a single school and a general store. PG&E dumped the chromium-laced water into a pond.

Lately there had been reports of problems with the neighbors' wells. PG&E had just drawn greenish water from one well and discovered high levels of chromium. Now, retired farmer John Speth was complaining of greenish deposits in his toilet bowl.

Jacobs took a look in the bowl but assured Speth that PG&E had nothing to do with it. "When I left Mr. Speth," Jacobs later wrote in **longhand** (https://www.documentcloud.org/documents/563689-intra-company-memo-re-john-speth.html) , "he was satisfied but still concerned about his water." Speth died of stomach cancer in 1974.

Key Findings

Tens of millions of Americans drink water contaminated with chromium (VI), a compound the Environmental Protection Agency was poised in 2011 to conclude likely causes cancer. That finding would set the stage for setting stricter drinking-water standards.

The National Toxicology Program, part of the National Institutes of Health, published a major rodent study in 2008 that concluded there was "clear evidence" chromium (VI) in water was a carcinogen.

The EPA's assessment of chromium was delayed to wait for new studies paid for by the American Chemistry Council, the chemical industry's main trade group and lobbyist.

Some of the same industry-paid scientists involved in past efforts to stall government action on chromium worked on the studies delaying the EPA.

After delays of nearly a decade, the California Environmental Protection Agency declined to wait for the industry studies and issued its own finding in 2011 that chromium was a carcinogen in drinking water.

The EPA initially planned to complete its chromium (VI) assessment in 2015. After the Center for Public Integrity and PBS NewsHour started asking questions about the delay, EPA posted a revised timetable for completing the assessment this year.

It wasn't until Dec. 7, 1987 — 22 years after that visit to Speth's house — that PG&E finally **told** (https://www.documentcloud.org/documents/563694-pge-cao-6-87-160-2.html) the local water board that it had contaminated the underground water. The company claimed it had discovered the problem just one week earlier.

From here, the story is familiar to anyone who saw the hit film *Erin Brockovich*. The corporate polluter was taken to court. The victims got millions of dollars. Problem solved.

But in reality, the “chromate problem” has not gone away. Today, **tens of millions** (http://www.ewg.org/chromium6-in-tap-water) of Americans drink chromium-tainted tap water. Yet the controversy over whether people like Speth are dying of cancer from it is still being hotly debated.

Some of the most powerful voices in the debate are companies with a stake in the outcome. They’ve hired scientists to convince regulators that the chemical compound is safe. The lawsuit that Brockovich championed was merely the beginning of an intriguing tale about corporate manipulation of science.

In 2008, the National Toxicology Program, part of the National Institutes of Health, published groundbreaking **research** (http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr546.pdf) detailing how mice and rats that drank heavy doses of a toxic form of chromium called chromium (VI) developed cancerous tumors. The findings prompted the Environmental Protection Agency to act.

EPA scientists evaluated hundreds of studies and concluded that chromium (VI) likely causes cancer in people who drink it. The agency in 2011 was on the verge of making its scientists’ findings official — a first step toward forming more stringent clean-water rules. But last year it bowed to pressure and **announced** (http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=221433) it was going to wait for new studies being paid for by the chemical industry.

To lead those studies, the American Chemistry Council, the industry’s main trade group and lobbyist, hired ToxStrategies Inc., a Texas-based firm with scientists experienced in poking holes in research that links chromium to cancer. The company describes its business this way on its website: “We often interact and collaborate with regulatory, academic and industrial professionals to ensure that the most appropriate science is incorporated into each assessment.”

Mark Harris and Deborah Proctor, two principal scientists at ToxStrategies, have a history of attempting to delay regulatory action on chromium. Starting in 1996, they were both leaders in the chrome industry’s efforts to dissuade the Occupational Safety and Health Administration from setting stricter rules for airborne chromium in the workplace. OSHA pushed back action for years despite decades of research showing that workers exposed to chromium were dying at higher-than-expected rates of lung cancer. The agency finally adopted a stricter standard in 2006 under pressure from a court order.

In part one of a two-part series, PBS NewsHour Science Correspondent Miles O'Brien travels to Hinkley, Calif. — the town whose multi-million dollar settlement for groundwater contamination was featured in the movie "Erin Brockovich." Now, almost 30 years later, O'Brien explores the reasons why the groundwater in Hinkley still has dangerous levels of the chemical chromium and its link to cancer.

Proctor also worked on revising a 1987 study that concluded that Chinese villagers who drank water polluted with chromium (VI) had higher than normal rates of stomach cancer. With funding from PG&E, Proctor's employer, ChemRisk, paid the Chinese author to help publish a new analysis of the data. In contrast to the earlier article, the new one concluded that chromium wasn't the likely culprit.The revised study — which did not reveal the involvement of PG&E or its scientists — helped persuade California health officials to delay new drinking water standards for chromium.

Finally, with industry funding, Proctor worked to try to influence the makeup and findings of a scientific panel deciding whether California needed stricter drinking water standards for chromium. The panel concluded — to the surprise of many — that there was no scientific basis for believing that drinking chromium causes cancer. One-third of Californians have chromium in their water.

Proctor and Harris declined to respond to requests for interviews.

The use of science to delay regulation is part of a familiar pattern in the field of environmental science. Industry pays for research to address "data gaps." Even when animals or people are believed to be getting cancer from exposure, industry scientists argue that the chemical in question is dangerous only at extremely high doses. Finally, they argue that you can't determine a safe dose of a chemical unless you understand precisely how it causes cancer. Until all the questions are answered, they say, it's not fair to ask industry to bear the cost of stricter rules.

"So now what is happening is the industry is trying to get scientists to slow down the EPA," said Gary Praglin, one of the lawyers who sued PG&E on behalf of Speth and hundreds of others who had lived near the Hinkley pumping station.

David Michaels, an epidemiologist who now heads OSHA, has written extensively about this brand of science.

"Their business model is straightforward," Michaels wrote in his book, "Doubt Is Their Product." "They profit by helping corporations minimize public health and environmental protection and fight claims of injury and illness. In field after field, year after year, this same handful of individuals come up again and again."

Overwhelming evidence of lung cancer

Suspicions that chromium might cause cancer emerged in the late 19th century. In the 1950s, studies of factory workers exposed to airborne chromium showed much higher rates of lung cancer than expected. Thomas Mancuso, a pioneer in occupational medicine, continued to follow the workers at a chromate plant in Painesville, Ohio, for decades. In his final **account** (http://www.ncbi.nlm.nih.gov/pubmed/9028428) in 1997, he reported that 23 percent of them had died of lung cancer. Other studies elsewhere confirmed Mancuso's findings.

Given the overwhelming evidence that chromium particles in the air were killing people, PG&E's challenge in the Hinkley case was to persuade judges on an arbitration panel that chromium traces in water were different. The company hired academic scientists, such as Steven Patierno at George Washington University, who testified that saliva and stomach acid render toxic chromium harmless, at least at levels that any human would drink.

Still, a few troubling studies at the time suggested that humans and animals may have developed cancer from drinking chromium. To address those studies, PG&E hired ChemRisk, a scientific firm that helped companies with legal or regulatory issues. The chief executive officer of ChemRisk was Dennis Paustenbach, a San Francisco scientist who has become the undisputed star of product defense.

Paustenbach declined interview requests. In a 2009 profile written by two University of Virginia professors, Paustenbach explains that he's been driven since his modest upbringing to be financially successful, putting in 65-hour work weeks.

His work as a scientist has included advocacy from the start. Each week as a young toxicologist at a chemical company in Connecticut, he flew to the nation's capital to lobby regulatory agencies such as the EPA. His relationship with the agency evolved and he later sat on

numerous EPA advisory panels. For the past four years, he's **served** (http://www.epa.gov/osp/bosc/exec-comm.htm) on a panel overseeing EPA research.

A rare inside look at what Paustenbach does can be found in the **minutes** (https://www.documentcloud.org/documents/605232-chrome-coalition-2-13-96.html) of a 1996 meeting in Pittsburgh of the Chrome Coalition, then the industry's trade group. At the time, OSHA was proposing a big reduction in the amount of chromium dust allowed in the workplace. Paustenbach outlined a plan to prevent that from happening.

"Dr. Paustenbach suggested that … the Coalition may wish to approach the regulators with a program designed to fill a 'data gap' … to forestall the rulemaking," the minutes read.

There was a discussion of ChemRisk possibly providing "confidential" and "pro bono" assistance to researchers at Johns Hopkins University to finish analyzing data for an EPA study of a Baltimore chromate plant. The EPA study was designed to answer questions left from Mancuso's earlier work. At the same time, Paustenbach proposed writing an "anti-Mancuso manuscript" and critiquing all relevant workplace studies in an "effort of convincing OSHA not to go forward with what they presently have."

Also attending the meeting were Proctor, who worked for Paustenbach at ChemRisk, and Harris, a former ChemRisk employee who at the time worked for Chemical Land Holdings, a company involved in a costly chromium cleanup. Both Proctor and Harris now work for ToxStrategies.

Paustenbach said in a recent statement to CPI and PBS NewsHour, "There is no evidence supporting any unethical conduct by ChemRisk scientist in regards to past work for the Chrome Coalition. The focus of ChemRisk scientists was solely on expanding the body of knowledge on which OSHA and other scientists could evaluate Chromium 6."

In the end, the **EPA study**

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(http://www.sciences.com/news/2009/GibbChromiumStudy.pdf) confirmed Mancuso's findings that workers exposed to chromium were at

a substantially higher risk of dying from lung cancer. Still, OSHA would wait more than a decade to tighten workplace standards for chromium under pressure from federal appeals court decision.

For the PG&E lawsuit, Paustenbach decided to conduct original research. Environmental science often lacks good human studies. Few people would volunteer to drink something potentially toxic to see if it would make them sick. Yet, that is precisely what Paustenbach did.

He and other scientists at ChemRisk sat for hours in Jacuzzis filled with chromium-laced water. They also drank chromium-contaminated water by the jug and then ran tests on their blood and urine.

ChemRisk scientist Brent Finley appeared on **ABC News** (http://abcnews.go.com/Nightline/video/1996-pge-investigation-15114900) in 1996 to drink some of the yellow water, prompting correspondent Cynthia McFadden to say, "There are those who would say you drinking a gallon of this chromium-laced water doesn't prove anything except that you — in some people's minds — may be foolish."

Paustenbach explained in his business school profile that he's motivated in his work by what he sees as greedy lawyers using bad science to take advantage of corporations.

"Without a doubt, a large percentage of environmental and occupational claims are simply bogus," he said, "intended only to extract money from those who society believes can afford to 'share the wealth.' "

Residents of Hinkley meet to discuss the contamination of their drinking water, a jug of which is seen here. PG&E is offering from buy scores of homes affected. Many of the townspeople don't trust the giant utility despite a massive cleanup effort. The meetings are often punctuated by angry outbursts.
Miles O'Brien, PBS NewsHour

Secrets of the 'Blue-Ribbon Panel'

Before the film Erin Brockovich even came out, the state of California was already taking steps to strengthen drinking-water standards for chromium. In 1999, scientists at the California Office of Environmental Health Hazard Assessment **concluded** (http://oehha.ca.gov/water/phg/pdf/chrom_f.pdf) that it was safe to assume that drinking chromium may cause cancer. They reasoned that breathing chromium was just another way the metal got into the body and caused damage. Plus, a 1968 study showed that 11 out of 66 female mice developed tumors after drinking chromium-laced water.

OEHHA's next task was to figure out how much chromium a person could drink each day without exceeding a one-in-a-million chance of getting cancer from it. The agency computed a number that was 40 times lower than the existing U.S. drinking-water limit.

One industry consultant warned that if this standard became law, it would cost $11 billion to clean up California's water, plus another $1.7 billion every year to keep chromium out of the water.

Before a new drinking-water standard could take effect, the state asked the University of California to set up a "blue-ribbon panel" of scientists to review the science. In August 2001, the panel issued a **report** (http://oehha.ca.gov/public_info/facts/pdf/crpanelrptfinal901.pdf) that said there was "**no basis** (http://www.oehha.ca.gov/public_info/facts/pdf/Chrom6press.pdf) " for concluding that chromium-contaminated water could cause cancer.

The panel dismissed the rodent study because an unrelated virus had killed many of the mice. It barely addressed the mounds of research on lung cancer.

The state agency concluded that it had little choice but to retract its chromium "public health goal" and wait. The state had asked the National Toxicology Program to do multimillion-dollar rodent studies on chromium. But the results wouldn't be published for another seven years.

Questions soon arose about whether the blue-ribbon panel was biased. When the group held its only public hearing in July 2001, a lawyer for Hinkley residents, Brian Depew, attended. Depew said an environmental activist approached him afterward and later sent him a binder of documents that touched off months of investigation by Depew's law firm.

The lawyers soon documented that Paustenbach initially served on the panel even though PG&E had paid ChemRisk at least $1.5 million during the lawsuits. Paustenbach said he didn't appear at the public hearing and his name is not on the report.

The lawyers also learned from invoices and testimony that Exponent, the company where Paustenbach served as vice president and its most senior scientist, was being paid by an industry group focusing attention on the blue-ribbon panel. The Alliance for Responsible Water Policy was bankrolled by General Electric Co. and Lockheed Martin Corp., two companies entangled in chromium cleanups.

A **strategic action plan** (https://www.documentcloud.org/documents/609039-newman-exh017.html#document/p6/a93328) for the Alliance dated April 6, 2001, and later disclosed in court records, listed as its strategy to "participate in state panel's review of chromium 6, influence selection of panelists [and] provide input and information to panel."

Proctor acknowledged in a deposition that she drew up a wish list of panelists and gave it to a lobbyist, Eric Newman. One of her colleagues, Brent Finley, also asked how he could get on the panel. Newman, who declined to comment for this story, responded to Finley in a March 31, 2001, **email** (https://www.documentcloud.org/documents/609040-finley.html) : "We will be lobbying hard for balanced representation. … It is critical that we get you, Deborah Proctor and/or other folks on the non-alarmist side of things."

According to Proctor's testimony, one of the names on her list was Joshua Hamilton, a Dartmouth professor working as an expert witness for PG&E. In 2011, Hamilton would be named to an EPA peer review panel for chromium (VI) and urge the agency to wait for new industry-funded studies led by Proctor. Hamilton, in a statement, has denied that he had any conflicts of interest while he served on the EPA panel.

When Paustenbach was named to the panel, Finley sent an **email** (https://www.documentcloud.org/documents/609040-finley.html) to Newman saying, "So, it looks like we got 'one of our own' on the panel."

When asked whether Exponent was being paid by an industry-funded group for work related to the blue-ribbon panel, Paustenbach told CPI through a public-relations firm, "I have heard that this is true, but I do not know specific details because I did not participate in any work for the Alliance."

Proctor, Paustenbach and other Exponent scientists quickly penned a **review article** (http://www.ncbi.nlm.nih.gov/pubmed/12028825) that could serve as a blueprint for the panel, and Paustenbach shared it with the group. The article was paid for by Merck, another company involved in a chromium **cleanup** (http://www.pharmalot.com/2011/04/former-merck-unit-polluted-air-groundwater/) . The panel chairman, Jerold Last, sent an **email** (https://www.documentcloud.org/documents/609450-last.html#document/p2/a94904) to the group on June 14, 2001, saying, "I copied the third chapter pretty much verbatim from a review Dennis and his colleagues have in press, so we will want to do some revisions to eliminate the verbatim aspect."

Paustenbach denied that the blue-ribbon panel's report was merely copied from Proctor's article. He told a California Senate committee investigating the panel that only "4 percent — exactly 4 percent — of the report was, in part, borrowed from a published paper by my colleague," Proctor. Last, who did not respond to requests for comment, told the committee that what "started out as cutting and pasting … ended up being material that one or all of us reviewed thoroughly before we put it into the report."

The major conclusions reached in the ChemRisk article and the state report were the same.

Paustenbach said that he disclosed his involvement in the PG&E lawsuit to Last but that neither he nor Last considered the PG&E work to be a conflict of interest. Still, because of concerns raised by an advocacy group, Paustenbach said he stepped down from the panel before

the panel held its public hearing.

When the blue-ribbon panel report came out, Paustenbach attached it to an **email** (https://www.documentcloud.org/documents/609038-paustenbach.html) to a colleague at Exponent saying, "Buy a good bottle of wine, pull up a chair, and then read this. Then say to yourself, 'Yep, I really finally did something good for society…' The world is now a better place to live."

When a lawyer read the email aloud during a deposition, another scientist who served on the panel called it "sad."

"This [is] about winning. It's not about truth," John Froines, a toxicologist at the University of California, Los Angeles, testified. "The world isn't a better place to live. The world is actually a poorer place to live because of this. It makes people cynical about trusting in the science, and I think that's really too bad."

Froines quit the panel before it finished its report, saying he was concerned about panelists with ties to industry. But also, Froines simply didn't believe the panel's findings.

In the early 1990s, PG&E bought up homes in the Hinkley neighborhood most affected by contaminated water. The company razed and burned some of the homes, but some boarded-up and abandoned buildings remain.
(Miles O'Brien, PBS NewsHour)

Chinese study revisited

Meanwhile, the California Environmental Protection Agency also had suspicions about the blue-ribbon panel.

Two studies highlighted in the panel report came from China's Liaoning province, northeast of Beijing, where a smelter began contaminating the water with chromium (VI) in 1965. A doctor in the area cared for the sick for years and eventually counted the deaths from cancer. He published an article in 1987 in a Chinese journal, concluding that villagers who drank the tainted water suffered higher rates of stomach cancer.

A decade later, the same doctor published a new article in an American journal concluding that chromium most likely wasn't the culprit.

The head of California EPA's Office of Environmental Health Hazard Assessment, George Alexeeff, asked a new epidemiologist on staff, Jay Beaumont, to look into the studies. In recent interviews, Beaumont said he quickly found things that didn't seem to add up.

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For example, the revised article said stomach-cancer rates for the province weren’t available. But Beaumont had a colleague quickly track down the data at the University of California, Berkeley, library. Beaumont said the numbers came from the same source the Chinese doctor used for other comparisons.

Within a few days, Beaumont ran his **own analysis** (https://www.documentcloud.org/documents/608824-jay-beaumont-reanalyzes-zhang-data.html) and found that villagers who drank chromium-laced water were 85 percent more likely to have stomach cancers than were those who lived in the surrounding province.

Beaumont tried to reach the Chinese author, Dr. Zhang JianDong, but he had died in 1999. However, there was still a website promoting a book Zhang had written. Something caught Beaumont’s attention. The **site** (https://www.documentcloud.org/documents/613079-zhang-web-page.html) revealed that Zhang was a consultant to McLaren/Hart Environmental Engineering Corp., the company that at the time owned ChemRisk.

Putting the pieces together, Beaumont wrote an **email** (https://www.documentcloud.org/documents/607604-reference27.html) to his boss, saying that “the money to pay Dr. Zhang likely came from the industrial clients of McLaren/Hart who have a strong financial interest in the health effects evidence for Cr6. I don’t know what Dr. Zhang was paid to do by McLaren/Hart, but republishing his study with different conclusions seems a possibility.”

PG&E now acknowledges it paid for the revised analysis, though **records** (https://www.documentcloud.org/documents/607605-reference37.html) show only about $2,000 went to Zhang.

Two ChemRisk documents describe Zhang’s role as “research assistance” and “document review and consultation.” Meanwhile, a ChemRisk scientist named project coordinator was **budgeted** (https://www.documentcloud.org/documents/608825-budget-for-pg-amp-e-zhang-study.html%22%20%5Cl%20%22document/p2/a94909) to be paid $13,500 to “interpret data” and “write reports” that were then to be edited by Paustenbach and Finley. The ChemRisk proposal **linked** (https://www.documentcloud.org/documents/608825-budget-for-pg-amp-e-zhang-study.html#document/p1/a94910) the research to the PG&E lawsuit by saying that the new article “can be used as the foundation of a number of trial exhibits that summarize the absence of the association between cancer and groundwater exposure to Cr6.”

Proctor, the same scientist who recently conducted studies for the American Chemistry Council, billed for her time on the Chinese article as well, according to a deposition.

“What was important to PG&E at the time is that the science was accurate,” said Sheryl Bilbrey, now in charge of the cleanup in Hinkley for PG&E. “So we did fund that work, and I think it’s unfortunate that when it was republished they didn’t acknowledge PG&E’s involvement,

because it really took away from the focus of the science and had more to do with the disclosure issue.

"PG&E's intention on any project is to make sure that we have the best science," Bilbrey said. "These projects are incredibly important to us, and we want to get it right. So we looked to Dr. Paustenbach and his experts to make sure that the science was accurate."

Paustenbach, through a public-relations firm, released a 9-page statement acknowledging that ChemRisk approached Zhang and another author to point out that "there were shortcomings in how these physicians interpreted their data." The statement said that Zhang was surprised by the new ChemRisk analysis but agreed with it. The firm also released hundreds of pages of documents that included **one** (https://www.documentcloud.org/documents/609091-zhang-agrees-to-manuscript.html) signed by Zhang saying he agreed to the "editing and expanding of the original manuscript."

Paustenbach's recent statement says, "The record makes clear not only that Zhang prepared the report, but also that Zhang, fearful of political pressure from his government, indicated that acknowledgment of American researchers was not appropriate since it was his study." Paustenbach testified in 2002, "We asked Dr. Zhang, in fact, to be coauthors on that paper for sake of transparency … Dr. Zhang, on his own decision, chose to keep that as a singular authorship."

None of the documents Paustenbach provided CPI indicate that Zhang explicitly objected to other names being listed as authors.

Despite the question of authorship, scientists at California's OEHHA said they took the new study at face value. Still, they rejected its findings.

"The '97 study basically concluded that there was no association between chromium (VI) in the drinking water and cancer cases among the Chinese villagers, in large part because the villages that were more distant from the source of the drinking water contamination had higher cancer rates," said Allan Hirsch, OEHHA's deputy director, in a recent interview. "People closest to the facility may not have been drinking the water, because it was yellow and unpalatable."

In a recent statement, Paustenbach characterized the California EPA's analysis as "flawed and incorrect."

The Journal of Occupational and Environmental Medicine retracted the article. Journal editor Paul Brandt-Rauf said in a recent interview with CPI that the article violated its policies by not revealing all of the significant authors or the funding.

Paustenbach said through a spokesman that the rules did not require disclosure because the amount paid Zhang was so small. However, Brandt-Rauf rejected that explanation.

The Environmental Working Group, an advocacy organization, did its own investigation of the Zhang study and was troubled by what it found. "I mean, this really is a story about science for sale," said Heather White, executive director of the group."It's shocking."

EPA faces industry pressure

In 2008, the National Toxicology Program published the results of its rodent studies. High numbers of the mice and rats developed tumors in their oral cavities and small intestines. The NTP concluded that there was "**clear evidence** (http://ntp.niehs.nih.gov/?objectid=E1C04561-F1F6-975E-7B21E8B231BAB44F) " that drinking chromium (VI) causes cancer. At about the same time, the California EPA took the nearly unprecedented step of publishing its own findings on the Chinese study.

Both the federal and California EPAs began preparing scientific assessments based on the new research. Both would come to the same conclusion. Hexavalent chromium is safe only in miniscule doses.

Yet the American Chemistry Council planned to have a number of new studies ready just before the EPA was scheduled to issue its final assessment. The ACC urged the EPA to wait until the agency could digest the new data. The scientists at ToxStrategies proposed studies to address "**data gaps** (https://www.documentcloud.org/documents/604991-comment-submitted-by-deborah-proctor-toxstrategies.html) " in the NTP study.

It was a move harkening back to the Chrome Coalition meeting in 1996 that Proctor and Harris attended. When she worked for Paustenbach, Proctor published a series of **articles** (http://www.chemrisk.com/publications/Proctor%20J%20Occup%20Environ%20Hyg%201%20752%202004.pdf) about workers in the same plant that Mancuso studied for decades, but her conclusion was quite different. Her **studies** (http://www.ncbi.nlm.nih.gov/pubmed/14641890) concluded that OSHA did not need to tighten its standard to protect workers.

In the end, OSHA adopted a stricter standard, but critics argue that it's still too high. By OSHA's own calculations, 10 to 45 workers out of 1,000 are expected to get lung cancer in their lifetimes from the current exposure limit.

The California EPA, which had already delayed a chromium assessment for a decade, refused to wait for ToxStrategies' studies, saying, "It would be very difficult for OEHHA to justify further delay."

California's assessment of chromium went through not one, but two peer-review panels. Some of the independent scientists questioned whether the safe-dose level was actually too high, so OEHHA lowered it. The agency **issued** (http://oehha.ca.gov/water/phg/pdf/Cr6PHG072911.pdf) its public-health goal on chromium (VI) in July 2011.

At first, the head of the EPA's chemical-assessment program, Vincent Cogliano, also **refused** (https://www.documentcloud.org/documents/551115-vincent-cogliano-to-acc.html) to wait for the ToxStrategies studies. But five of nine peer reviewers selected by a private contractor urged delay. One of the reviewers was Steven Patierno, a former PG&E expert witness who served as a consultant on the ToxStrategies' studies.

In January, the NTP published new **research** (http://www.ncbi.nlm.nih.gov/pubmed/23334696) from its rodent studies that challenges Patierno's contention that saliva and stomach acids render chromium (VI) completely harmless, undermining the theory that chromium is dangerous only in high doses.

Celeste Monforton, a professorial lecturer at George Washington University's School of Public Health who has written about industry scientists' influence on chromium policy, said that, based on her own experience working with agencies, regulators are aware that research done by industry is often an attempt to delay.

"Some people at EPA understand that and know that," she said. "It takes the political will to stand up to that."

In the Hinkley lawsuit, judges more 16 years ago considered the scientific arguments and ruled against PG&E. In essence, they concluded that the contaminated water in Speth's toilet was capable of causing cancer.

Froines, the UCLA scientist who resigned from the blue-ribbon panel, said it's time for public health agencies to do the same.

"At this point, we shouldn't be debating the carcinogenicity. … We should be at a place where we're looking for alternatives to the use of chromium," said Froines, who has evaluated more than 400 chemicals for a California advisory panel he chairs. "You're dealing with people's lives."

Miles O'Brien, science correspondent for the PBS NewsHour, contributed to this story

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NATURAL RESOURCES DEFENSE COUNCIL

Comments from NRDC on EPA's TSCA Systematic Review
EPA-HQ-OPPT-2018-0210

Comments on the application of the TSCA Systematic Review to the Exposure and Use Assessment and Human Health and Environmental Hazard Summary for Five PBT Chemicals
EPA-HQ-OPPT-2018-0314

August 16th, 2018

Comments supported by the following:

Alaska Community Action on Toxics (Pamela Miller)
Beyond Pesticides (Nichelle Harriott)
Biomonitoring Resource Center (Sharyle Patton)
Center for Biological Diversity (Nathan Donley)
Center for Environmental Health (Ansje Miller)
Citizens' Environmental Coalition (Barbara Warren)
Clean Water Action (Lynn Thorp)
Environmental Health Strategy Center (Patrick MacRoy)
Environmental Working Group (Melanie Benesh)
Friends of the Earth (Dana Perls)
Glynn Environmental Coalition (Rachael Thompson)
Healthy Babies Bright Futures (Charlotte Brody)
Healthy Building Network (Tom Lent)
International Center for Technology Assessment (Jaydee Hanson)
Made Safe (Amy Ziff)
Safer Chemicals Healthy Families (Liz Hitchcock)
Science and Environmental Health Network (Ted Schettler)
Sierra Club (Sonya Lunder)
Women's Voices for the Earth (Erin Switalski)

The Natural Resources Defense Council (NRDC) is a national, non-profit environmental organization of lawyers, scientists, and other professionals. NRDC presents these comments on behalf of our over three million members and online activists. NRDC does not have any financial interest in the topic of these comments.

Overview

The EPA TSCA program recently made public its approach for conducting its chemical assessments, called the "Application of Systematic Review in TSCA Risk Evaluations" (TSCA Systematic Review, May 2018, EPA Document# 740-P1-8001). See EPA's website for details.

A Systematic Review Protocol or Framework is *supposed to be* a systematic and transparent method to evaluate the quality of evidence and to support evidence-based decision making. With environmental health science, it is frequently the case that single studies have limits that make them insufficient on their own to provide reliable answers. Regulators, lawmakers, researchers, product manufacturers, and others want chemical assessments based on an evaluation and synthesis of all the evidence. This can include whole animal studies, cellular and in vitro studies (test tube and petri dish studies), and wide-ranging human data. All these study types have strengths and limitations; a systematic way to collect all the relevant information, assess the quality and reliability of each study, and then integrate all the studies together will lead to the most accurate assessment. A Systematic Review is a meant to be a systematic and transparent method to evaluate the quality of data and to support evidence-based decision making.

Unfortunately, the TSCA Systematic Review document is less about evaluating the quality of evidence, and more about eliminating it altogether. The document is incomplete, inconsistent with the state of the science, and too flawed to be used. Accordingly, use of the document violates TSCA and is otherwise arbitrary and capricious.

Given the serious flaws with the TSCA systematic review, it should not be used for any chemical assessments at EPA or any other agency. We are particularly concerned that in addition to chemicals being reviewed under TSCA, EPA is using it to assess the five PBT chemicals now under review. We therefore request that EPA consider the concerns detailed in these comments for its Exposure and Use Assessment and Human Health and Environmental Hazard Summary for Five PBT Chemicals (EPA-HQ-OPPT-2018-0314-0001).

We detail our main concerns below.

TSCA Systematic Review must be formally and rigorously peer reviewed

It is deeply concerning that the TSCA systematic review is already being applied to the TSCA chemicals, [1] including the ten chemicals that are the subject of these comments. It is still under development and has not been vetted by the EPA Science Advisory Board or any other appropriate scientific peer review committee, and has not undergone any public peer review, scientific scrutiny, or public comment before this comment period. This violates existing EPA peer review requirements as described in the EPA Peer Review Handbook (4th Edition, 2015), and the Final Information Quality Bulletin for Peer Review (OMB, 2004).[2] The Handbook and Bulletin require documents that are "highly influential," "novel, controversial, or precedent-setting," or have "significant interagency interest" to undergo peer review before being implemented. The peer review process that EPA should undertake if it is intending to use the TSCA Systematic Review should be transparent, include inter-agency input, and be accountable to the recommendations that arise from that process as described in the EPA Handbook and OMB Bulletin.

Since the TSCA Systematic Review has not undergone a formal rigorous transparent scientific review process yet, it would be inappropriate to apply it to any EPA chemical assessments at this time. Use of the document is procedurally flawed, and arbitrary and capricious.

Inconsistent or in conflict with state of the science

As pointed out in the comments here, and those of the University of California San Francisco Program on Reproductive Health and the Environment (UCSF PHRE) experts, the TSCA Systematic Review document seems to lack any linkages to the established worldwide leaders on systematic review. For example, it departs in significant and disturbing ways from approaches advanced by: National Academy of Sciences recent favorable review of the EPA IRIS program (NRC 2018);[3] the National Toxicology Program (NTP);[4] the international scientific collaboration that developed a framework for the "systematic review and integrated

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[1] Application of Systematic Review in TSCA Risk Evaluations. May 2018. EPA Document# 740-P1-8001.Docket ID EPA-HQ-OPPT-2018-0210

[2] OMB Final Information Quality Bulletin for Peer Review. M-05-03. December 2004

[3] National Academies of Sciences, Engineering, and Medicine. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press. https://doi.org/10.17226/25086.

[4] National Toxicology Program. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. In: U.S. Department of Health and Human Services, editor.: Office of Health Assessment and Translation, Division of National Toxicology Program, National Institute of Environmental Health Sciences; 2015

assessment" (SYRINA) of endocrine disrupting chemicals;[5] and the Navigation Guide systematic review method (NavGuide) developed by a collaboration of scientists led by the University of California San Francisco.[6] In fact, in many critical ways the TSCA Systematic Review is in direct conflict with these and other established Systematic Review frameworks, as detailed in these comments and comments from UCSF PHRE to this docket.

Additionally, the TSCA Systematic Review is not harmonized with major hazard identification approaches described by the IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, California OEHHA chemical assessment approaches, and other globally-harmonized hazard ID approaches that enjoy widespread acceptance among the environmental health community. Accordingly, the TSCA Systematic Review violates Section 26(h) of TSCA requiring EPA to employ best available science when implementing Section 6 of the law.

The purpose of having a harmonized system is to promote common, consistent criteria for classifying chemicals according to their health, physical and environmental hazards, and to encourage the use of compatible hazard labels, material safety data sheets for workers, and other hazard communication information based on the resulting classifications, thus improving health protection.

The TSCA program should utilize a Systematic Review method that is already established, and that reflects the state of the science on systematic review, such as the NTP-OHAT or NavGuide methods.

TSCA Systematic Review shares similar problems with EPA's discredited Science Transparency Rule

Although the TSCA Systematic Review fails to align with established chemical assessment methods, it does manage to dovetail disturbingly well with the discredited Science Transparency Rule,[7] characterized by Reuters as a "concession to big business that has long requested such restrictions".[8] For reasons detailed in these comments, both the Censor Science rule and the TSCA Systematic Review would make it hard or impossible for EPA to

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[5] Vandenberg LN, Ågerstrand M, Beronius A, Beausoleil C, Bergman Å, Bero LA,Bornehag CG, Boyer CS, Cooper GS, Cotgreave I, Gee D, Grandjean P, Guyton KZ, Hass U, Heindel JJ, Jobling S, Kidd KA, Kortenkamp A, Macleod MR, Martin OV, Norinder U, Scheringer M, Thayer KA, Toppari J, Whaley P, Woodruff TJ, Rudén C. A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals. Environ Health. 2016 Jul 14;15(1):74. Review.

[6] Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect. 2014 Oct;122(10):1007-14. doi:10.1289/ehp.1307175. Epub 2014 Jun 25. Review.

[7] Strengthening Transparency in Regulatory Science, April 2018 RIN 2080–AA14. EPA–HQ–OA–2018–0259.

[8] U.S. environment agency proposes limits to science used in rulemaking. Valerie Volcovici, Timothy Gardner. Reuters, April 24, 2018. Available online at https://www.reuters.com/article/us-usa-epa-science/epa-set-to-unveil-policy-barring-secret-science-sources-idUSKBN1HV2DJ

include important human health and toxicology studies it its chemical hazard assessments if there is any information that is missing or not made public. Ultimately, both documents will hamstring EPA's use of scientific information, which will severely harm EPA's work quality and public credibility by producing inaccurate unprotective EPA chemical assessments. Both documents violate Sections 26(h) and (k) of TSCA by excluding valid scientific data from EPA's Section 6 risk evaluation process. See comments by NRDC submitted to Docket EPA-HQ-OA-2018-0259, incorporated here by reference.

Below we highlight some of the most serious problems with the TSCA Systematic Review:

Reporting quality is used as a false proxy for study quality

The systematic framework is almost wholly reliant on reporting as a measure of study quality, when in fact reporting and quality are not the same and are not even necessarily correlated. What information and how much is reported can be highly variable, depending on whether a study is published in a high-ranking generalist journal like Science or Nature with very severe space limits, or a discipline-specific journal like Environmental Health Perspectives that encourages lengthy descriptions of methods and results. Government reports may require even more detailed reporting, or less. And, conventions in reporting have changed over time, and especially with online journals having much less restrictive space constraints than even only a decade ago. Reporting differences will depend on the expected audience, where information needs and expectations between researchers and regulators can differ dramatically. The TSCA Systematic Review will not accurately determine study quality, as currently written.

For example, the TSCA Systematic Review's data screening approach to inclusion and exclusion criteria for identifying information relevant to the risk evaluation process includes seven bullet points, but only one that describes human health hazard data, and it contains only one simple requirement, that the data "meet minimum reporting elements" (TSCA SR Section 2.2.2. p. 22-23). In the flawed TSCA Systematic Review, failure to report some information will result in eliminating entire human health and environmental hazard studies. The whole approach appears to be designed to eliminate non-industry studies that do not have to adhere to regulatory reporting preferences or requirements.

The TSCA Systematic Review uses reporting in the Tables on data quality criteria for each data stream:

- For environmental fate assessments (see Table C-9, p. 51), almost every one of the eight domains in the first column – test substance, test design, test conditions, etc. – includes a statement that if some aspect of that domain is not reported, it would render the study unusable: "The study did not include or report control groups"; "The test method was not reported"; "Equilibrium was not established or reported", etc. Any one of these failures to report information is considered by the TSCA Systematic Review to be a "serious flaw that would make fate data unacceptable for use in the fate assessment". Presumably all studies with any one or more of these reporting gaps would be immediately and totally excluded from further consideration.

- Similarly, among the lengthy list of "serious flaws that would make epidemiological studies unacceptable" (TSCA SR Table H-8, p. 231) the failure to report on almost any aspect of the study is grounds for exclusion. If "Exposure variables were not well defined, and sources of data and detailed methods of exposure assessment were not reported" a study is excluded. If "Numbers of outcome events or summary measures, or diagnostic criteria were not defined or reported" a study is excluded. If "There are known [sample] contamination issues and no documentation that the issues were addressed" a study is excluded.
- Any epidemiology study of any type is scored as "unacceptable" for use in exposure assessment if "exposure misclassification is present and likely to impact results, but no attempt is made to address it" (TSCA SR Table E-13, p 120). This is despite the fact that many exposure misclassifications make it harder to detect a real effect (bias to the null, leading to false negatives); if an effect is observed it is therefore more likely to be real.

There is no evidence that any of these above reporting gaps would lead to reduced study quality, or an unacceptably high risk of bias. In fact, many of these things would lead to the discarding of reliable evidence of harm. For example, observational wildlife and epidemiology studies have many methodological features that tend to bias the direction of error away from detecting a real effect (bias to the null, leading to false negatives): nondifferential exposure misclassification, inadequate follow-up, lost cases, and simple models that fail to capture realistic complexity in the system.[9] Many excellent studies demonstrating links between environmental exposures and adverse health effects will be discarded under the TSCA Systematic Review, resulting in an inaccurate and unprotective chemical assessment.

Instead of simple reporting, established standards like NavGuide and NTP use more sophisticated and biologically sensitive systems for evaluating studies. For example, they recognize that an epidemiology study may be confidently used for developing an ever/never exposure analysis, but less so for a dose-response curve. It would be important to consider a study like this for making a determination about whether an agent is linked to elevated cancer risk, for example, instead of considering it 'unusable' with the TSCA Systematic Review approach.

<u>Bias against rare health outcomes – example of TCE cardiac effects</u>

Because the TSCA Systematic Review is structured to give studies a poor grade or designate them as low confidence without regard to biological understanding of the study outcome, the TSCA Systematic Review will result in discarding studies with particularly rare health outcomes. This conflicts with other established study assessment approaches that take into consideration that there may be *greater* confidence in an outcome due to the rarity of the effect, even with some study weaknesses. For example, the EPA Cancer Guidelines recognize this, and elevate the significance of rare tumors as follows:

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[9] Gee D. Late Lessons from Early Warnings: Toward Realism and Precaution with Endocrine-Disrupting Substances. Environmental Health Perspectives. 2006;114(Suppl 1):152-160. doi:10.1289/ehp.8134.

- The Guidelines indicate that even a study with some limitations due to bias or confounding can be elevated if the adverse outcome endpoints are rare: "A unique feature that can be ascribed to the effects of a particular agent (such as a tumor type that is seen only rarely in the absence of the agent) can increase sensitivity by permitting separation of bias and confounding factors from real effects" (p. 2-10);
- The Guidelines require a (more lenient) lower statistical significance level for rare tumors, as compared to common tumors, recommending: "a statistical significance of 1% for common tumors or 5% for rare tumors" (p. 2-20);
- The Guidelines directs that a chemical should be classified as, "Likely to Be Carcinogenic to Humans" with evidence of a rare animal tumor response, even if it is in only "a single experiment that is assumed to be relevant to humans" (p. 2-55).

The TSCA Systematic Review fails to account for the significance of rare adverse outcomes in studies with limitations or a lower statistical significance. We are particularly concerned that the EPA Toxics Office plans to use its Systematic Review to discard the scientific evidence linking the rare outcome of congenital heart defects with trichlorethylene (TCE). The heart effects are rare but can be disabling or even deadly. Based on a transparent systematic review of the scientific evidence, EPA scientists determined that there were some uses of TCE in consumer and industrial products that were so dangerous they should be discontinued.[10] In particular, EPA scientists had raised concerns with low-dose exposures during pregnancy that could lead to permanent heart malformations in the developing fetus.[11]

However, recently the ToxStrategies consulting firm published a list of biases with the TCE heart studies that it contends should make the study unusable for regulatory purposes. Its analysis and conclusion follow the criteria laid out in the TSCA Systematic Review. Significantly, ToxStrategies received funding from Entek International, whose Oregon-based battery parts operations have been repeatedly fined for violations related to its TCE pollution including allegedly poisoning its workers (The Oregonian, May 5, 2017).[12] Thus, ToxStrategies itself also had a financial bias – something that the TSCA Systematic Review does not include in the risk of bias analysis, as discussed further below.

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[10] Regulation of Certain Uses under Toxic Substances Control Act: Methylene Chloride and N-Methylpyrrolidone. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0231-0001

Regulation of Certain Uses under Toxic Substances Control Act: Trichloroethylene. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0163-0001

Regulation of Certain Uses under Toxic Substances Control Act: Trichloroethylene; Vapor Degreasing. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0387-0001

[11] Trichloroethylene (TCE); Regulation of Certain Uses Under TSCA §6(a). December 2016. Pg 11-12. Docket EPA-HQ-OPPT-2016-0163. Available at https://www.epa.gov/sites/production/files/2016-12/documents/prepubcopy_tce-aerosolspotting_nprm_frdocument_2016-12-06.pdf

[12] Chemical linked to Entek air pollution also linked to employees' health problems. Rob Davis. The Oregonian. Updated May 5, 2017; Posted Apr 29, 2017. https://www.oregonlive.com/environment/index.ssf/2017/04/chemical_linked_to_entek_air_p.html

Instead of using reporting criteria to exclude studies, the EPA TSCA program should adopt an existing systematic review method that adheres to current state of the science, which dictates that reporting elements should be included in a risk of bias analysis through all the domains, not establishing a reporting requirement that would disqualify a study. Sections 26(h) and (k) of TSCA require such an approach.

TSCA Systematic Review is biased to score industry-sponsored studies higher than they deserve

As detailed in the previous section, by its heavy and inappropriate use of reporting criteria to exclude studies from a chemical assessment, the TSCA Systematic Review will provide an open door to regulatory studies sponsored by financially conflicted parties. This is because the only studies required to meet specific reporting requirements are the Guideline studies that are conducted for the purpose of gaining regulatory approval of products, and these are sponsored by the industry that has a financial interest in commercializing its product. The reporting requirements are described as Good Laboratory Practices (GLP). Neither Guideline methods nor GLP-compliance is necessarily associated with study quality; it may in fact be a very poor-quality study – but well reported - as described below.

Guideline studies are most often designed to identify major toxic effects (apical effects) like cancer, major organ weight gain or loss, body weight gain or loss, skeletal malformations, loss of fur, tremors and convulsions, diarrhea, and obvious signs of lethargy. However, by the time these major (apical) endpoints are observed, significant toxicity has already occurred. This is because Guideline studies must follow methods that are established over years of negotiated process between regulatory agencies and the regulated community, and thus almost by definition simply cannot reflect modern methods for evaluating chemicals. Guideline studies aren't designed to grapple with the issues of low-dose exposures, formulations and chemical mixtures, endocrine or hormonal effects, and subtle but significant neurobehavioral impacts like what are now known to be caused by even very low doses of lead during critical windows of development. In summary, Guideline studies are designed to observe obvious and significant toxicity, not to identify early warnings (upstream indicators) of potential harm, such as reduced anogenital distance which is a predictor of later-life infertility.

Good Laboratory Practices (GLP) establish standards for animal care and data collection and reporting. Guideline studies must be GLP-compliant. The GLP standards were established for industry laboratories in response to serious widespread fraudulent practices documented by government inspectors in the 1970s. This is why it is a requirement only for industry-sponsored studies. To be GLP compliant, studies must adhere to specified approaches to recordkeeping to facilitate audits and reduce fraud (54 Fed. Reg. 34034 Aug. 17, 1989). Since the requirements are primarily about reporting, and not study methods, the GLP requirements are not necessarily associated with higher quality research, proper study design or correct statistical analysis.[13] In

[13] Myers, J. P., F. S. vom Saal, et al. (2009). "Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A." Environ Health Perspect 117 (3): 309-15.

many cases GLP and Guideline studies are not published, not subjected to public scientific scrutiny, and not independently peer reviewed.

Rather than being subject to GLP and Guidelines requirements, all academic research studies must instead adhere to the established standards of Institutional Review Boards (IRB) for both ethical and scientific conduct.[14] Like many aspects of GLP guidelines, IRB's ensure that the studies are conducted according to established and evolving best practices and legal requirements for animal care, human subject protections, and other ethical practices. However, unlike GLP, the IRB does not mandate specific reporting requirements. And, unlike Guideline studies which hamstring researchers into pre-set methods, IRB review will provide guidance to ensure sound research design while also encouraging cutting edge and exploratory research using novel methods to advance scientific knowledge.

The TSCA Systematic Review is inherently problematic and will yield poor-quality results by relying on criteria that favor regulatory studies over hypothesis-driven research.

In some places, the TSCA Systematic Review masks its bias towards reporting criteria. For example, it recommends that after the overall score is applied to a study, the final determination of study quality can be adjusted through use of the ToxRTool (TSCA SR p. 31, 34). However, since the ToxRTool was developed to assess the reporting quality of a study, its use simply perpetuates the existing flaws in the TSCR Systematic Review (the reliability categories utilized in the ToxRTool are the same as the Klimisch codes of reliability, developed over two decades ago by BASF employees).[15] Since the Klimisch codes favor Guideline and GLP studies, then using ToxRTool would be subject to the same criticism as over-relying on either Klimisch codes, Guideline studies or GLP – simply put, they are a measure of reporting, not of study quality.

<u>Use of scoring – an approach discredited by experts</u>

The TSCA Systematic Review is in direct conflict with best practices for systematic review by applying a scoring system to studies, and particularly to develop a "composite" quality score across all studies. It has been documented that the use of scoring in this manner will inevitably lead to a bias in study evaluation, based on pre-determined weighting strategies that fail to account for the complexity of study design, study conduct, how the study is being used, and other features. For example, authors published in JAMA reported that, "Our data indicate that the use of summary scores to identify [clinical] trials of high quality is problematic."[16] A medical journal review article titled, "No role for quality scores in systematic reviews of diagnostic

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[14] More information about IRBs here: https://www.niehs.nih.gov/about/boards/irb/index.cfm

[15] Klimisch HJ, Andreae M, Tillmann U. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul Toxicol Pharmacol. 1997 Feb;25 (1):1-5

[16] Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999 Sep 15;282(11):1054-60.

accuracy studies" Concludes that scoring systems do not produce higher quality assessments; they simply don't work.[17] A recent publication of 29 collaborators on new tools to assess risk of bias in systematic review specifically emphasized that they, "should not be used to generate a summary 'quality score' because of the well-known problems associated with such scores".[18]

The US Institute of Medicine recommended standards for conducting high-quality systematic reviews that specifically warn against scoring systems, and particularly against ones relying on reporting: "Quality scoring systems have not been validated. Studies assessed as excellent quality using one scoring method may be subsequently assessed as lower quality using another scoring method (Moher et al., 1996).[19] Moreover, with an emphasis on risk of bias, the Systematic Review more appropriately assesses the quality of study design and conduct rather than the quality of reporting."[20]

In summary, experts warn against the scoring system promoted in the TSCA Systematic Review. The current state of the science for evaluating clinical and environmental health research is to describe or document each component of the assessment tool separately, without trying to calculate an overall numeric score. In accordance with Section 26(h)(and (k) of TSCA, EPA must use an existing Systematic Review method that adheres to these scientific standards, such as the NTP or NavGuide Systematic Review methods.

TSCA Systematic Review fails to include a comprehensive risk of bias analysis

EPA's TSCA Systematic Review does not address financial or other conflicts of interest at all, despite widespread acknowledgement across the scientific and medical community that regulated industry sponsorship can lead to biased study design, biased study conduct, and biased reporting of study results – all leading to a favorable outcome for the regulated industry sponsor.[21]

The National Toxicology Program Systematic Review states that, "It may be useful to pay attention to author affiliations and funding source which can contribute to selective outcome reporting when results are not consistent with expectations or value to the research

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[17] Whiting P, Harbord R, Kleijnen J. No role for quality scores in systematic reviews of diagnostic accuracy studies. BMC Med Res Methodol. 2005 May 26;5:19. Review.

[18] Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B, Davies P, Kleijnen J, Churchill R; ROBIS group. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016 Jan;69:225-34. doi:10.1016/j.jclinepi.2015.06.005. Epub 2015 Jun 16.

[19] Moher D, Jadad AR, Tugwell P. Assessing the quality of randomized controlled trials. Current issues and future directions. Int J Technol Assess Health Care. 1996 Spring;12(2):195-208. Review.

[20] Eden J., Levit L., Berg A.O., Morton S., editors. Finding what works in health care: standards for systematic reviews. The National Academies Press; Washington, D.C: 2011.

[21] Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2017 Feb 16;2:MR000033.
https://www.ncbi.nlm.nih.gov/pubmed/?term=10.1002%2F14651858.MR000033.pub3

objectives."[22] The Agency for Healthcare Research and Quality recommends that: "(1) at a minimum, EPCs [Evidence-based Practice Centers] should routinely report the source of each study's funding; (2) EPCs should consider issues of selective outcome reporting at the individual study level and for the body of evidence; and (3) EPCs should conduct sensitivity analyses for the body of evidence when they have reason to suspect that the source of funding or disclosed conflict of interest is influencing studies' results".[23] Consideration of funding bias should be considered standard practice in all EPA systematic reviews, yet is wholly absent from the TSCA Systematic Review approach.

There is recognition that financial bias is most evident in industry-sponsored studies that are conducted to gain regulatory approval. For example, a survey of the pharmaceutical company funding on clinical research concluded that, "Bias in favour of industry is apparent in every one of the themes examined with the result that research funded by industry undermines confidence in medical knowledge."[24] Medical journals are extremely concerned about industry-bias leading to poor quality or even inaccurate studies, and have worked hard to tighten up their disclosure requirements for authors, peer reviewers, and even editors of journals. The Institute of Medicine includes an extensive discussion of the problems of financial conflict in its report on systematic review, citing recommendations of the International Committee of Medical Journal Editors that highlight relationships with commercial entities as of concern. [25] [26]

Yet, despite the tremendous global effort that biomedical and other journals have undertaken to require study authors to disclose financial interests, because it is a recognized source of potential bias, the TSCA Systematic Review and other government Systematic Review methods continue to ignore this information in an analysis of bias.
Considerations of funding from the regulated industry must be included in a comprehensive risk of bias analysis in any systematic review method that is used for TSCA chemical assessments. This would be consistent with recommendations of the National Academies review of the IRIS program: "funding sources should be considered in the risk-of-bias assessment conducted for systematic reviews that are a part of an IRIS assessment".[27]

[22] NTP Systematic Review risk of bias tool. https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf

[23] Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov

[24] Lexchin J. Sponsorship bias in clinical research. Int J Risk Saf Med. 2012;24(4):233-42. doi: 10.3233/JRS-2012-0574.

[25] Eden J., Levit L., Berg A.O., Morton S., editors. Finding what works in health care: standards for systematic reviews. The National Academies Press; Washington, D.C: 2011. p. 52

[26] Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. ICMJE, 2010.

[27] National Research Council. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. P. 79 https://doi.org/10.17226/18764

TSCA Systematic Review is incomplete

The evidence integration process is a critical part of a systematic review method. It describes the selection of a hazard identification category. For example, NTP has the following hazard categories: known, presumed, suspected, and not classifiable. There is a narrative that accompanies each of these categories. The hazard identification categories used by NTP are comparable to those used in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Both the NTP and NavGuide systematic review methods are designed to effectively address the full range of data relevant to environmental health assessments (e.g., human, animal, and in vitro/mechanistic studies), and include tools to assess potential bias of studies.

However, although the TSCA Systematic Review discusses how to evaluate (and score) individual studies, it has no method for integrating different streams of evidence to make a risk determination. The TSCA Systematic Review explains that this is because its timeframe for conducting its assessments has been compressed, and it has simply not completed the development of its systematic review protocols (TSCA SR, Section 3.1, p. 19). EPA writes that the data integration portion of the method is still under development.

Among many disturbing elements of this document is the fact that it is acknowledged to be both incomplete and already being applied to the chemicals under review. Even more unsettling is the disturbing claim in the TSCA Problem Formulation documents that the TSCA program plans to undo years of work by EPA IRIS and other programs by subjecting the ten TSCA chemicals to a re-do using this just-released TSCA Systematic Review method. This exclusion of valid scientific information based upon an incomplete and deeply flawed TSCA Systematic Review Method is a serious, immediate, and ongoing violation of Section 26(h) and (k) of TSCA, and the Administrative Procedures Act.

Inappropriate and inaccurate use of mechanistic information

We support the TSCA Systematic Review insofar as it indicates that mechanistic information is not necessary for interpreting or evaluating other data: "Although highly preferred, the availability of a fully elucidated mode of action (MOA) or adverse outcome pathway (AOP) is not required to conduct the human health hazard assessment for a given chemical." (TSCA SR, p. 172). This is consistent with the EPA Cancer Guidelines: "A lack of mechanistic data, however, is not a reason to reject causality" (EPA Cancer Guidelines, p. 2-14).[28]

We are concerned, however, that the chemical industry and its paid consultants have been arguing for over a decade that MOA conclusions be rendered separately from other data

[28] EPA 2005. Guidelines for Carcinogen Risk Assessment EPA/630/P-03/001B. https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf

streams, as if it were stand-alone information (see, for example, Meek et al 2003).[29] This is also the approach in the TSCA Systematic Review: "EPA/OPPT plans to prioritize the evaluation of mechanistic evidence instead of evaluating all of the identified evidence upfront. This approach has the advantage of conducting a focused review of those mechanistic studies that are most relevant to the hazards under evaluation." (TSCA SR p. 172). This is in direct contradiction with the EPA Cancer Guidelines, which state that mechanistic data, "are incorporated into the context of all of the data regarding weight of the evidence for carcinogenicity" (EPA Cancer Guidelines, p. 2-39).[30] The TSCA Systematic Review is therefore in conflict with EPA Guidelines which are peer-reviewed and finalized, and inconsistent with Section 26 of TSCA.

We are additionally concerned that the TSCA program may prematurely and inappropriately rely on some of the new tools in hazard, exposure, and risk assessment that have developed rapidly over the last decade. For example, EPA's Toxicity ForeCaster (ToxCast™) is billed by EPA as its "most updated, publicly available high-throughput toxicity data on thousands of chemicals".[31] The chemical screening results from ToxCast are shared by EPA with the inter-agency collaboration called Toxicology in the 21st Century (Tox21) which includes EPA, NIH, and FDA. Federally sponsored programs like Tox21[32] have exponentially increased the amount of molecular information available for environmentally-relevant chemicals. While there are important potential benefits to faster, cheaper testing methods for evaluating environmental chemicals, their ultimate usefulness resides in their ability to be protective of the health of populations and ecosystems. To be fully protective, TSCA requires these non-animal methods to be (1) scientifically reliable, (2) relevant, and (3) capable of providing information of equivalent or better scientific reliability and quality to that which would be obtained from vertebrate animal testing. Reliability, relevance, and providing equal or better information than vertebrate tests represent independent criterion that must be established prior to their use in lieu of whole-animal based tests. The overzealous deployment of tests that may underestimate or completely miss toxicity or exposure (high false negative rate) would result in risk evaluations and determinations that are not consistent with the requirements of the revised TSCA – particularly for vulnerable populations including children, pregnant women and workers. Non-animal test methods and strategies must be proven to be reliable, relevant, and able to provide information of equivalent or better scientific reliability and quality prior to being included on a list of acceptable tools to aide decision making.

We are additionally concerned that much of the methods and raw data for ToxCast and Tox21 are generated by outside contractors including private for-profit entities that are holding

[29] M Meek ME, Bucher JR, Cohen SM, Dellarco V, Hill RN, Lehman-McKeeman LD, Longfellow DG, Pastoor T, Seed J, Patton DE. A framework for human relevance analysis of information on carcinogenic modes of action. Crit Rev Toxicol. 2003;33(6):591-653. Review.653.

[30] EPA 2005. Guidelines for Carcinogen Risk Assessment EPA/630/P-03/001B. https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf

[31] EPA website on Toxicity ForeCaster (ToxCast™) Data. Accessed 5/24/2018. https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data

[32] https://ntp.niehs.nih.gov/results/tox21/index.html

portions of the models and raw data as proprietary. For example, a private company called BioSeek is contracted to EPA to use its proprietary BioMAP® system to generate ToxCast data.[33] [34] According to a 2012 article, "The new agreement [with EPA] covers the use of BioSeek's unique BioMAP® Systems human primary cell assay platform to help predict the biological activity and potential toxicity of up to 60,000 additional samples, including environmental chemicals, pesticides, failed pharmaceuticals and nanomaterials... Under the agreement, BioSeek will receive up to $46,770,000 over the next five years for testing up to 60,000 samples. The specific value of the award will depend on the volume of testing required during the contract period. The company's previous contract with the EPA awarded in 2007 was for up to $12.8 million over five years..." [35] In addition to BioSeek, some cell-based assays run by Odyssey Thera, Novascreen, Attagene and other contractors also used a proprietary process, where the raw data and models are not fully disclosed to the public.[36] The proprietary nature of tests and data supporting the ToxCast and Tox21 platforms means that the entire platforms are not fully transparent.

A major challenge in using any of these methods to test for chemical toxicity is that different systems can react to chemicals in different ways. These differences should not be used to dismiss evidence of toxicity. In fact, strong evidence from mechanistic/MOA studies could support a conclusion and raise it to a level of increased concern. The TSCA program should rely on a Systematic Review method such as NTP or NavGuide that provides a robust credible method for integrating multiple streams of data, including mechanistic information, to elevate the level of concern with a chemical hazard.

When information is missing or unreliable, EPA should use established defaults that will protect health, and set stringent criteria for when to depart from health-protective defaults

The TSCA Systematic Review is noticeably silent on the issue of health-protective default assumptions. When information is missing or unreliable, the framework should be clear and consistent that its approach is to use scientifically-based default assumptions that will protect health to improve the timeliness of the chemical assessment and decision-making process, and

[33] Powerpoint presentation. BioSeek - ToxCast Phase I Project Update. Ellen Berg, PhD, BioSeek, Inc. EPA Chemical Prioritization Community of Practice. Monthly Meeting January 24, 2008. https://www.epa.gov/sites/production/files/2014-08/documents/bioseek_toxcast_summary_24jan08.pdf

[34] BioSeek Awarded New Five-Year Contract from EPA ToxCast™ Program: Up to 60,000 Additional Samples to be Screened Using BioSeek's BioMAP® Systems. Oct 04, 2012 from BioSeek, LLC. Accessed 5/24/2018. https://www.prnewswire.com/news-releases/bioseek-awarded-new-five-year-contract-from-epa-toxcast-program-172642451.ht

[35] BioSeek Awarded New Five-Year Contract from EPA ToxCast™ Program: Up to 60,000 Additional Samples to be Screened Using BioSeek's BioMAP® Systems. Oct 04, 2012 from BioSeek, LLC. Accessed 5/24/2018. https://www.prnewswire.com/news-releases/bioseek-awarded-new-five-year-contract-from-epa-toxcast-program-172642451.ht

[36] Kleinstreuer NC, Ceger P, Watt ED, Martin M, Houck K, Browne P, Thomas RS, Casey WM, Dix DJ, Allen D, Sakamuru S, Xia M, Huang R, Judson R. Development and Validation of a Computational Model for Androgen Receptor Activity. Chem Res Toxicol. 2017 Apr 17;30(4):946-964.

set clear scientifically-based criteria for when to depart from these assumptions.[37] In the landmark "Science and Decisions" report (NAS, 2009), the NAS committee concluded that, "established defaults need to be maintained for the steps in the risk assessment that require inferences."[38] The NAS committee recommended that EPA and other agencies update default factors and assumptions based on the best current science, identify where unstated or implicit assumptions are used, and replace these with explicit assumptions wherever possible. These recommendations push Agencies to, "continue and expand use of the best, most current science to support or revise its default assumptions,"[39] making the assumptions stronger, rather than reducing reliance on them. In fact, the committee specifically recommended that EPA develop "clear standards for departures from defaults."[40] The committee also noted that establishing, "clear criteria for departure from defaults can provide incentives for third parties to produce research" that can reduce uncertainty and, over time, result in more accurate assessments. Importantly, by using the established defaults more often, EPA could avoid "the delay entailed by having to re-examine generic information with every new risk assessment."[41] EPA should also evaluate and quantify, when possible, the impact of the uncertainty associated with a default assumption, including a description of how using a default versus the chosen alternative assumption affects the decisions that protect the environment and public health.

EPA should keep the scientific and regulatory work of TSCA in separate offices

EPA should keep chemical assessments in the science office with the EPA staff that have established expertise in this area. A recent National Academies report of the IRIS chemical assessment program specifically supported current best practices recommended by the Institute of Medicine that, "the IRIS teams involved in the systematic-review process should be independent of those involved in regulatory decision-making who use the products of the systematic-review teams. The committee notes that the current organizational structure of the IRIS program in the EPA Office of Research and Development is consistent with those best practices."[42] Placing chemical assessments within the OCSPP regulatory office will compromise the independence and public trust in the final product.

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[37] NRDC Issue paper. Strengthening toxic chemical risk assessments to protect human health. S Janssen, J Sass, T Schettler, G Solomon. February, 2012. http://switchboard.nrdc.org/blogs/jsass/nrdc_issue_paper_better_risk_a.html

[38] Science and Decisions: Advancing Risk Assessment. National Research Council of the National Academies. (2009), p. 7.

[39] NRC 2009 Science and Decisions, p. 207.

[40] NRC 2009 Science and Decisions, p. 199.

[41] NRC 2009 Science and Decisions, p. 191.

[42] National Academies of Sciences, Engineering, and Medicine. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press. Page 8. https://doi.org/10.17226/25086

In summary, EPA should heed the recommendations of the National Academies and leave the IRIS program with its independence, and the resources and ability to do its work without political interference by the regulated industries whose toxic chemical products are being assessed.

Conclusion

A Systematic Review Protocol or Framework is *supposed to be* a systematic and transparent method to evaluate the quality of evidence and to support evidence-based decision making. Fundamentally, however, the TSCA Systematic Review document describes a head-in-sand approach to any evidence that a toxic chemical is toxic. Such evidence will be excluded from further consideration by the TSCA program, to almost guarantee that the resulting chemical assessment will be as chemical-friendly as possible, enabling chemical manufacturers to avoid restrictions and regulations and dodge legal liability. The TSCA Systematic Review is incomplete, in conflict with best practices and the state of the science, and in conflict with recommendations from the IOM and National Academies. It is too flawed to be used, and EPA's application of the document in its current form constitutes a serious, immediate, and ongoing violation of TSCA and the Administrative Procedures Act.

We recommend that the EPA TSCA program employ an existing credible peer-reviewed Systematic Review method that conforms with the state of the science, such as the National Toxicology Program Systematic Review, or the Navigational Guide. This is consistent with recommendations from the National Academies and other expert scientific reports.

We also recommend that the EPA TSCA program use existing assessments from the IRIS program and continue to support the IRIS program with independence and resources adequate for it to complete its mission, including conducting chemical assessments for the TSCA program. This is consistent with recommendations from the 2018 National Academies in its recent favorable review of the IRIS program.[43]

Thank you for the opportunity to provide comments.

Respectfully,

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[43] National Academies of Sciences, Engineering, and Medicine. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press. https://doi.org/10.17226/25086

Exhibit C

https://roanoke.com/news/local/ferc-study-finds-no-risk-from-protective-coating-of-mountain-valley-pipeline/article_09559b96-ae27-5f32-b0ee-46f69f75f47c.html

FERC study finds no risk from protective coating of Mountain Valley Pipeline

Laurence Hammack
Oct 8, 2020

A chalky substance is visible on Franklin County landowner Anne Bernard's fingers. She worries that a protective on the section of pipe has been exposed to the elements and could be degrading into the nearby water and soil more than a year of study, the Federal Energy Regulatory Commission found no basis for the fears about the epo coating on the Mountain Valley or the Atlantic Coast pipelines.

The Roanoke Times | File 2019

Laurence Hammack

Segments of steel pipe stockpiled along the path of a natural gas pipeline, exposed to the elements for two years while lawsuits delayed construction, pose no risk to the surrounding air, soil or water, a federal agency has concluded.

In a report released Thursday, the Federal Energy Regulatory Commission addressed concerns that have been raised about the Mountain Valley Pipeline.

An epoxy coating applied to protect the pipe from corrosion may have released toxins in two ways, the theory goes: into the air after it degenerates from sitting too long in the sun, and into groundwater after the 42-inch diameter pipe is assembled and buried.

But after more than a year of study, FERC found no basis for the fears about Mountain Valley or the Atlantic Coast Pipeline, a similar project that collapsed in July under the weight of multiple legal challenges.

The report cites the conclusion of ToxStrategies, a consulting firm hired by Atlantic Coast, that there should be “no impact on human health or the environment from the chalky residue” that forms on the pipes after prolonged exposure to sunlight.

After getting the report last year, FERC requested more information, including an assessment of pipeline storage yards. A revised study dated Aug. 27 reached the same conclusion as the first.

In a letter Thursday to Virginia Health Commissioner Norman Oliver, FERC said it also considered citizen comments, information from the two pipelines and the coating’s manufacturer, and input from the U.S. Centers for Disease Control.

Oliver and David Paylor, director of the Virginia Department of Environmental Quality, requested last year that FERC provide additional information on the possible risks of the coating, citing citizen concerns.

Those concerns still exist.

The report "provides no reassurance for the public based on these inadequate assessments," said Tina Smusz, a retired physician and assistant professor of medicine from Montgomery County who has been following the issue.

For example, she said, the CDC's Agency for Toxic Substances and Disease Registry said the environmental samplings taken by ToxStrategies were not sufficient "to fully evaluate the public health concerns associated with the gas pipe/storage area."

Soil samples collected from an Atlantic Coast storage yard in West Virginia found chemicals in small enough concentrations not to pose a risk to people who regularly came into contact with the soil.

However, the CDC agency for toxic substances said it was unclear if the chemicals had entered nearby public water supplies , or whether people would be exposed to airborne hazardous materials released from the pipes.

Dominion Energy, one of the lead partners in the Atlantic Coast Pipeline, requested the study last year, well before it announced in July that the project was being canceled. However, concerns remain about pipes that have yet to be removed from construction sites or storage areas.

Mountain Valley has already buried the pipe along 238 miles of its 303-mile route, the study stated, "so the novel circumstance of pipe exposed for multiple years is not as prevalent."

Smusz and others — including the Natural Resources Defense Council — have called for more investigation of the risks posed by the pipeline coating, 3M Scotchkote Fusion-Bonded Epoxy 6233.

Once chalking occurs, they say, carcinogens can be released into the air or, after the pile is buried, they can leach through soil and into groundwater, possibly contaminating private wells or public water supplies.

But the substance is "thousands of an inch in thickness," and any leaching that occurs does not release chemicals in amounts large enough to present a public danger, the ToxStrategies report stated.

The maker of the coating, 3M Manufacturing Co., told The Roanoke Times last year that the coating is safe if applied properly and allowed to fully cure. "We are not aware of any evidence to suggest that chalking is harmful to human health," it said in an email.

Mountain Valley has also said that it is unaware of any evidence of risks posed by the coating, which has been in use since the 1960s on many projects, including drinking water systems.

Concerns about the fusion-bonded epoxy coating are just one of many raised by pipeline opponents. The $5.7 billion project is overbudget and behind schedule, in large part due to legal challenges over erosion on steep mountain slopes during construction.

Opponents say the pipeline has blemished scenic views, clogged streams with sediment and endangered protected wildlife.

The Blue Ridge Environmental Defense League announced Thursday that Roanoke County has forwarded to DEQ its request that Mountain Valley be required to amend its stormwater management plans.

FERC is currently considering two requests from Mountain Valley. One is to lift a stop work order, now that two key permits have been restored. The other is to extend by two years an overarching approval that will otherwise expire Oct. 13.

Laurence Hammack

Laurence Hammack covers environmental issues, including the Mountain Valley Pipeline, and business and enterprise stories. He has been a reporter for The Roanoke Times for more than three decades.

Exhibit D

EXHIBIT
Britt-3

Expert Report of Janice K. Britt, Ph.D.

In the matter of:
In re: Valsartan, Losartan, and Irbesartan Products Liability MDL
United States District Court for the District of New Jersey

AUGUST 2, 2021

ToxStrategies
Innovative solutions
Sound science

Expert Report of
Janice K. Britt, Ph.D.

In the matter of:
In re: Valsartan, Losartan, and Irbesartan Products Liability MDL

United States District Court for the District of New Jersey

AUGUST 2, 2021

PREPARED ON BEHALF OF ALL DEFENDANTS

PREPARED BY:
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Acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
AE	adverse events
AI	acceptable intake
API	active pharmaceutical ingredient
ARB	angiotensin II receptor blocker
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
$BMDL_{10}$	benchmark dose (lower confidence limit)
CAS	Chemical Abstracts Service
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act (Superfund)
COC	chemical of concern
CPDB	Carcinogenic Potency Database
CPNP	1-Cyclopentyl-4-nitrosopiperazine
DNA	deoxyribonucleic acid
EMA	European Medicines Agency
EPA	US Environmental Protection Agency
ERT	European Registered Toxicologist
ETS	environmental tobacco smoke
EUROTOX	Federation of European Toxicologists & European Societies of Toxicology
FAERS	FDA Adverse Events Reporting System
FDA	U.S. Food and Drug Administration
FSRB	Fellow of the Royal Society of Biology
HR	hazard ratio
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
LADD	lifetime average daily dose
LOD	limit of detection
LTL	less-than-lifetime
MCL	maxiumum contaminant level
MeNP (MNP)	1-methyl-4-nitrosopiperazine
MNP	methyl-4-nitrosopiperazine, 1
MTD	maximum tolerated dose
NDEA	*N*-nitrosodiethylamine
NDMA	*N*-nitrosodimethylamine
NNK	4-(n-nitrosomethylamino)-1-(3-pyridyl)-1-butanone
NNN	*N*-nitrosonornicotine
NOAEL	no-observed-adverse-effect level
NOCs	nitrosamines
NRC	National Research Council
NSRL	no-significant-risk level
NTP	National Toxicology Program
OEHHA	Office of Environmental Health Hazard Assessment

OSWER	Office of Solid Waste and Emergency Response
PAH	polycyclic aromatic hydrocarbons
PDE	permitted daily exposure
PHG	public health goal
POD	point of departure
RfD	reference dose
SDWA	Safe Drinking Water Act
SOT	Society of Toxicology
TD_{50}	dose that resulted in a 50% tumor incidence
TEAM	Total Exposure Assessment Methodology (studies)
TNA	total *N*-nitrosamines
USDA	U.S. Department of Agriculture
USDHEW	U.S. Department of Health, Education and Welfare
VOC	volatile organic carbon
VSD	virtually safe dose
WHO	World Health Organization

Executive Summary

In this matter, the plaintiffs, through their experts, are arguing novel hypotheses that rely on many uncertainties, assumptions, and unknowns. The acceptance of these premises, without the proper scientific evidence and proof, not only violates the scientific method one uses to determine the specific cause of diseases, but its acceptance becomes a self-defeating hypothesis. Accepting these premises means there are literally hundreds, if not thousands, of other potential chemical causes of the alleged disease(s) that now cannot be excluded objectively using a proper specific causation analysis. The reasons for this conclusion are summarized in this executive summary.

The facts set forth below are based on my personal knowledge and are true and correct to the best of my knowledge. I present herein the types of facts and data that I and other experts in the field of toxicology reasonably rely upon. The opinions set forth herein represent my opinions expressed to a reasonable degree of scientific certainty. My opinions regarding this matter are based on the materials I reviewed, my education, my experience in toxicology, my knowledge of the toxicity of the chemicals at issue, and my understanding of proper and well-accepted methods for assessing exposure, dose, and risk (e.g., including but not limited to consideration of exposure, dose, and dose-response).

At present, in my opinion, the information that the plaintiffs' experts have submitted thus far consists of arguments that represent numerous theoretical possibilities that lack the evidence and rigorous proof of being a known chemical cause of the different alleged cancers. So, by lowering the evidence necessary to meet the scientific method for general causation, the plaintiffs' experts make the final decision a logical impossibility, because their logic can be applied to literally thousands of other chemicals to which the plaintiffs, as well as the general population, have been exposed.

In the main body of this report, I discuss the following subjects in more detail, as these are the bases for the preceding opinions.

No scientific body has concluded that the nitrosamines in question are human carcinogens, nor that they are known to cause in humans all of the cancers implied by plaintiffs' experts. While it is true that nitrosamines are rodent carcinogens, it is scientifically misleading to imply that the outcome of rodent tests can necessarily be applied to all other species and all other doses. The limitations of the chronic animal bioassay used to test chemicals for carcinogenic activity are numerous and have long been recognized. In fact, decades ago, Robert Squire, then the head of the government agency performing these tests, was among the first to outline some of these limitations (Squire, 1984). Because the testing regimen takes years to perform and is expensive, animals are typically given the maximum tolerated dose (MTD), and a second dose that is some fraction of the MTD. While using doses such as these maximizes the sensitivity of this test so that negative responses are not likely to represent a false negative because the dose tested was too low, it also creates pathophysiologic conditions in the animal that are so specific to the testing regimen (species tested, dose, tested, duration of test and dose, etc.) that they can be extrapolated to other species and doses only by using unproven assumptions. All toxic responses are a function of the species tested, the dose tested, and the duration of exposure and observation

period. Assessments of the chemicals tested to date for carcinogenic activity have demonstrated the following facts. First, it is believed that approximately 50% of chemicals (be they synthetic, natural, or medicinal) tested using this regimen will have carcinogenic activity at the relatively high doses that are used for this toxicity test. This is because the toxicities attendant with such high doses introduce numerous pathophysiologic changes that can increase tumor incidence indirectly (secondary to other biologic changes). So, to assume that animal carcinogenicity is sufficient evidence for disease causation in humans would imply that literally hundreds of other chemicals to which we are exposed on a routine or daily basis are also candidate causes. Second, as the dose is reduced from the MTD, the carcinogenic response can be lost. This means that the dose-response curve is steep, and other evidence has accumulated indicating that all carcinogenic responses, even those induced by mutagenic/genotoxic chemicals, are non-linear and threshold dependent. So, as the dose is lowered, it falls below the threshold for one or more key mutagenic or nonmutagenic events that produce the cancer in animals, and the risk becomes zero. Therefore, translating a real carcinogenic risk to humans at doses that pose a lower theoretical risk in animals is nothing more than speculation. Third, the chronic bioassay typically involves the use of test species with high background rates of cancer in organs where the carcinogenic response is frequently observed. It is common to not see the same carcinogenic response in another animal test species whose organs have lower background tumor rates. In fact, even though the rat and the mouse are far closer phylogenetically to each other than they are to humans, the evidence for positive carcinogenic activity in the mouse correlates poorly to the same finding in the rat, and the reverse is also true. Moreover, the positive carcinogenic responses, when seen, do not affect the same organs/tissues in these two species. Again, assuming that a chemical inducing cancer in one organ in a rodent species can be accurately correlated to a similar organ risk in humans is again speculation based on many unproven assumptions. For these reasons, and others, to assume that animal responses at high doses reflect the same responses in humans at lower doses is without proper scientific foundation and proof. To be able to properly assume that a chemical might cause cancer in humans at a lower dose requires statistically significant epidemiologic evidence to demonstrate that the chemical does, in fact, cause cancer in humans, and does so in a specific organ under specific dose and exposure conditions, before it can be considered to be a medically and scientifically believable possibility to consider.

In this matter, a number of the plaintiffs' experts discuss or provide numerical estimates of *risk*, with risk here meaning the chance or probability of contracting the disease. This term is often confusing to lay persons, because regulatory agencies long ago co-opted the term "risk"—which physicians and epidemiologists apply only to known causes of disease (epistemic risk factors, known causes of human disease) and applied the term "risk" to the theoretical possibilities observed in animal toxicity tests (nomologic risk factors, a biological possibility or unknown relevance to the human condition). The regulatory community inadvertently created this confusion, because they needed to create acceptably safe exposure limits for the many chemical exposures under their purview. In their situation, the use of the precautionary principle to varying extents (e.g., making worst-case assumptions where causal information was lacking or unclear) was acceptable, because they were tasked with ensuring the safety and protection of the public's health. For this purpose, then, making simplified biological or toxicological and mathematical assumptions

gave regulators a protective mechanism for determining an acceptably safe exposure level in the absence of clear proof or data. Regulatory and regulatory-like risk assessments for animal carcinogens use many assumptions and have numerous limitations. First, conservative approaches are adopted that are likely to numerically overstate the risk rather than underestimate it, in keeping with their health-protective mandates. However, even regulatory agencies like the U.S. Environmental Protection Agency (EPA), the governmental agency with the greatest experience with chemical risk assessments, recognizes that, while the number for animal carcinogens represents a theoretical, upper-bound estimate, the true human risk is likely to be much lower, if not zero, at the doses they believe represent the acceptably safe dose range. Because of the many assumptions adopted and their use of animal data, the EPA also recognizes that such "risk" estimates are not reliable or true estimates of human disease rates and cannot be used to predict whether an exposure has caused an individual's disease. In short, their risk assessment procedures are protective of human health but not predictive of human disease occurrence or rates. Other agencies or scientific groups adopting EPA-like models and extrapolations are subject to the same inherent limitations.

Additionally, when the plaintiffs' experts apply animal evidence of carcinogenicity and/or risk estimates from such data, they unintentionally make all other animal carcinogens also likely candidate causes. As stated earlier, with approximately only half of the chemical exposures of any kind (i.e., industrial/synthetic, natural, medical) that are expected to have carcinogenic activity tested, there exist many known and unknown carcinogenic exposures. Thus, as I illustrate in the report below, this introduces many chemicals of equivalent or greater theoretical risk that represent alternative potential causes of the plaintiffs' alleged diseases. These alternative causes have not been considered and eliminated by plaintiffs' experts. And these alternative chemical causes involve both endogenous (formed or originated in the body) and exogenous (formed or originated outside of the body) sources of nitrosamines, in addition to the hundreds of other classes and types of chemical carcinogens to which we are exposed.

In my report, I discuss the different risk assessment approaches that have been applied to the nitrosamine impurities in valsartan. As I explain, the initial approach used a crude TD_{50} approach, whereas, in my opinion, the more recent analysis by Johnson et al. (2021) represents the better, though still conservatively protective, risk assessment approach. The risks calculated by Johnson et al. (2021) are small and fall within the acceptably safe theoretical risk range long applied by the EPA. In fact, the EPA typically adopts a risk range of 1 in 10,000 to 1 in 1,000, 000 (or 1×10^{-4} to 1×10^{-6}) as the acceptable risk range for individual chemical exposures, and there are numerous examples of risks of this size posed by the chemicals that we routinely breathe, drink, ingest with food, or absorb dermally. This is an important finding, because risks this small are *not* expected to be a cause of any individual's cancer, given that other theoretical and real risk factors will always pose a far greater mathematical probability of causing the cancer. It is also for this and related reasons that the approach taken by plaintiffs' experts is flawed. And again, plaintiffs' experts have not considered the far larger source of endogenous nitrosamines, nor the other sources of exogenous nitrosamines, nor the other chemical carcinogens that are ubiquitous in our environment (see my discussion of common environmental exposures to chemical carcinogens). Instead, they have focused on a single, isolated exposure and

implied that this low risk was somehow meaningful, while ignoring the far greater risks from other carcinogenic exposures that we all incur. The other known causes of cancer are not trivial, as Sir Richard Doll, the famed cancer epidemiologist credited for establishing the smoking cancer link, long ago noted when he determined that diet, lifestyle choices, and other factors pose our greatest risk of developing cancer. In this vein, I would also note that the drug in question is used predominantly in older patients to prevent a serious cause of death, hypertension. Thus, the plaintiffs' exposure to the drug occurs after their decades of exposure to other carcinogenic chemicals and sources of nitrosamines.

To summarize, the plaintiffs and their experts in this case ask us to consider a single chemical exposure in isolation and to ignore the numerous chemical exposures we all incur in our daily home and work environments. Some of these other chemicals are also animal carcinogens (and in some cases, known human carcinogens), as well as the numerous environmental chemicals, as yet untested, but also likely to produce cancer in animals. Thus, the approach argued by plaintiffs' experts is to adopt assumptions and suppositions as though they were facts, when in fact they are not. The bases of the above opinions are discussed in greater detail in my report below.

1 Qualifications

I am currently a Managing Scientist at ToxStrategies, Inc., a firm that specializes in toxicology and the assessment of chemical exposures and their associated hazards or risks. I have more than 20 years of experience in toxicology and have worked in the areas of human and animal toxicology, chemical exposure assessment, dose-response analysis, and risk assessment. I also have extensive experience in the areas of systematic review, causation analysis, and Evidence-Based Toxicology. I recently published a 10-year retrospective on the use of evidence-based methods in assessing causation in toxicology. I have critically evaluated the toxicity of numerous chemicals, pharmaceuticals, dietary supplements, food and beverage products, consumer products, and medical devices. I have evaluated exposures involving hazardous waste sites, environmental contamination situations, consumer product exposures, and occupational and agriculture-related product exposures. I have also performed site-specific risk assessments, developed toxicological profiles for various chemicals, and evaluated the appropriateness of various regulatory toxicity criteria (e.g., reference doses, cancer slope factors, and occupational exposure guidelines).

I am currently serving as a member of the EPA's Human Studies Review Board, a federal advisory committee that provides advice and recommendations on issues of human subject research. I have also served as a toxicologist for the State of Florida in its Department of Agriculture and Consumer Services, where I worked in the Bureau of Pesticides and advised other divisions within the Department. In this capacity, I reviewed toxicity data and assisted in making regulatory decisions regarding the registration of pesticides for the State of Florida. As part of my work, I helped develop a regulatory procedure for ranking pesticides according to their chronic toxicity and leaching potential, with this procedure indicating those pesticide hazards that have the greatest potential to adversely affect groundwater resources. This procedure is now part of the peer-reviewed literature. I have

a bachelor's degree in Zoology from Texas A&M University and a doctorate in Toxicology from Texas A&M College of Veterinary Medicine and Biomedical Sciences. I am a member of the Society of Toxicology, the Society for Risk Analysis, the American Conference of Governmental Industrial Hygienists (ACGIH), and EUROTOX. In addition, I am a European Registered Toxicologist (ERT) and a fellow of the Royal Society of Biology (FSRB). Additional details of my experience, credentials, and a list of my publications are contained in my *curriculum vitae*.

2 Case-Specific Materials I Have Received

I have reviewed the documents listed below, among others, specific to this case.

2.1 General Materials

- Class Action Complaint – Robert Kruk et al. v. Zhejiang Huahai Pharmaceutical Co., Ltd., et al. (Civil Action No. 2018 cv 5944)
- Master Personal Injury Complaint – In re: Valsartan Products Liability Litigation (MDL No. 1:19-md-2875)
- Consolidated Amended Economic Loss Class Action Complaint – In Re: Valsartan Products Liability Litigation (No. 1:19-md-2875-RBK)
- Consolidated Amended Medical Monitoring Class Action Complaint – In Re: Valsartan Products Liability Litigation (No. 1:19-md-2875-RBK)
- Confidentiality Order entered by the Court in this matter
- Plaintiffs' Disclosure of Cancer Types
- CV and Report of Stephen S. Hecht, Ph.D. (July 6, 2021)
- CV and Report of Stephen M. Lagana, MD (July 26, 2021)
- CV and Report of Mahyar Etminan, Pharm.D., Sc.D. (July 6, 2021)
- CV and Report of David Madigan, Ph.D. (undated)
- CV and Report of Dipak Panigrahy, M.D. (July 6, 2021)
- FDA's Laboratory Analysis of Valsartan Products Website

2.2 Zhejiang Huahai Pharmaceutical Co., Ltd., Materials

- Periodic Safety Reports for Abbreviated New Drug Applications (ANDAs) 204821 (Valsartan Tablets) and 206083 (Valsartan and Hydrochlorothiazide Tablets)
- Zhejiang/Prinston US Food and Drug Administration (FDA) Meeting Request (June 18, 2018)

- Zhejiang/Prinston Response to FDA Questions (July 8, 2018)
- FDA Memorandum of Meeting Minutes (July 9, 2018)
- Zhejiang/Prinston FDA Meeting Package
- Testing Results for *N*-Nitrosodimethylamine (NDMA) and *N*-Nitrosodiethylamine (NDEA) for Zhejiang/Prinston
- Report of Charles Y. Wang, Ph.D. (June 15, 2018)

2.3 Aurobindo Materials

- Response to FDA General Advice Letter with Annexure-1
- Letter from Aurobindo to Lantech, dated April 1, 2019
- Aurobindo Toxicology Health Hazard Assessment
- Response to FDA-483 Issued February 9, 2019, to Unit XI
    - Initial Response
    - First Update
    - Second Update
- Initial Response to Warning Letter to Unit XI
    - Attachment 1: Assessment report on Valsartan Process-II
    - Attachment 3: Valsartan Investigation Report
    - Attachment 6: NDMA and NDEA testing results of materials sourced from Lantech
    - Attachment 10: Addendum to investigation report
    - Attachment 13: Test results of NDMA and NDEA for Valsartan & Olmesartan
- Documents cited in Plaintiffs' Expert Reports produced by Aurobindo
- Testing Results for NDMA and NDEA for Aurobindo
- Aurolife's Finished Dose Testing (Auro-MDL 2875-0113985)
- Aurobindo Pharma Ltd.'s Finished Dose Testing (APL-MDL 2875-0139456)

2.4 Mylan Materials

- Testing results for NDMA and NDEA for Mylan (MYLAN-MDL2875-00895544)
- Medical Risk Assessment for Valsartan Tablets and Caplets (MYLAN-MDL2875-00029585)

- Toxicology Assessment of NDMA and NDEA in Valsartan (MYLAN-MDL2875-00301525)

2.5 Teva Materials

- Testing results for NDMA and NDEA for Teva
- Toxicology Reports and Assessments
- TEVA Health Hazard Assessments, Valsartan Containing Products

3 My Understanding of the Case

My understanding of this case is that the plaintiffs and their experts are alleging exposure to nitrosamine impurities—*N*-nitrosodimethylamine (NDMA; CAS# 62-75-9) and/or *N*-nitrosodiethylamine (NDEA; CAS# 55-18-5)—contained in the drug substance (also known as Active Pharmaceutical Ingredient, or API) valsartan and/or the generic prescription drug product (also known as finished dosage form) medication incorporating valsartan API [manufactured by Zhejiang Huahai Pharmaceutical Co., Ltd. (Zhejiang/Prinston), Hetero Labs, Ltd., Mylan Laboratories, Ltd., Teva Pharmaceuticals, Torrent Pharmaceuticals, and Aurobindo Pharma, Ltd.]. The plaintiffs are stating that their exposure to NDMA and/or NDEA from these products caused them to develop certain cancers or put them at risk of developing cancers in the future.

Valsartan, and other "sartans" belong to the angiotensin II receptor blockers (ARBs) class of drugs that are used to treat hypertension (high blood pressure) and heart failure. ARBs are one of four classes that are used for the initial treatment of hypertension, which is present in ~46% of all adults in the United States, 76% of adults aged 65–74 years, and 82% of adults aged 75 years and older (Mann et al., 2021).

- On July 13, 2018, the U.S. Food and Drug Administration (FDA) issued a news release on a voluntary recall of several drug products containing the active pharmaceutical ingredient (API) valsartan, due to the presence of the impurity NDMA. The FDA recommended that patients consult with their physicians but keep taking valsartan until their health-care provider prescribes a replacement product: "Because valsartan is used in medicines to treat serious medical conditions, patients taking the recalled valsartan-containing medicines should continue taking their medicine until they have a replacement product." FDA stated in its press release that Zhejiang Huahai had stopped distributing its valsartan API and that FDA was working with the affected companies to eliminate or reduce the valsartan API impurity from future products. Based on subsequent investigation, other manufacturers of valsartan also issued voluntary recalls. Recalled products included:
    - Valsartan from Aurobindo Pharma Ltd., Hetero Labs, Ltd., Mylan Pharmaceuticals Inc., Prinston Pharmaceutical, Torrent

Pharmaceuticals, Major Pharmaceuticals, Solco Healthcare, Teva Pharmaceuticals

  - Amlodipine/valsartan combination products from Aurobindo Pharma Ltd., Mylan Pharmaceuticals Inc., and Teva Pharmaceuticals
  - Valsartan/hydrochlorothiazide combination products from Aurobindo Pharma Ltd., Princeton Pharmaceutical, Mylan Pharmaceuticals, Teva Pharmaceuticals, Solco Healthcare
  - Amlodipine/valsartan/hydrochlorothiazide combination products from Teva Pharmaceuticals, and Torrent Pharmaceuticals (FDA, 2018a,b).

- On July 24, 2018, the FDA again reminded consumers to continue taking their medication until receiving a replacement and noted the dangers of untreated hypertension and heart failure: "FDA reminds consumers to continue taking your current medicine until your doctor or pharmacist gives you a replacement or a different treatment option. Untreated hypertension (high blood pressure) leads to an increase in the risk of heart attacks and stroke. Untreated heart failure increases the risk of hospitalization and death" (FDA, 2018b).

- Valsartan was recalled by other regulatory agencies in 2018—e.g., European Medicines Agency (EMA) and the Danish Medicines Agency (Snodin and Elder, 2019).

- On August 26, 2020, two other medications, rifampin and rifapentine, were reported by the FDA to contain nitrosamine impurities. These two medications are antibacterial drugs used to treat tuberculosis. Rifampin is also used to treat and prevent other serious infections. The FDA stated that patients taking either of these medications should continue taking their current medications and consult with their health-care provider about any concerns they may have. FDA further stated that, to avoid shortages, they would not object to certain manufacturers temporarily distributing rifampin [containing 1-methyl-4-nitrosopiperazine (MNP or MeNP, CAS# 16339-07-4)] or rifapentine [containing 1-cyclopentyl-4-nitrosopiperazine (CPNP, CAS# 61379-66-6)] above the acceptable limits of 0.16 ppm and 0.1 ppm, respectively, or below 5 ppm MNP and 20 ppm CPNP. The FDA stated that, because tuberculosis is a potentially fatal disease, the risk of not taking these medications outweighs any potential risks from MNP or CPNP (FDA, 2021a). FDA states that hundreds of millions of patients have taken these tuberculosis medications over time and that it is possible these nitrosamines have been undetected in these medications for years or decades (FDA, 2020, 2021a).

- On July 2, 2021, Chantix™ (varenicline), a smoking cessation medication, was voluntarily recalled due to the presence of a nitrosamine impurity—*N*-nitroso-varenicline. The FDA stated that it would not object to certain manufacturers temporarily distributing varenicline tablets containing concentrations of *N*-nitroso-varenicline above FDA's acceptable intake limit of 37 ng/day of *N*-nitroso-varenicline but below the interim acceptable intake (AI) of 185 ng/day *N*-nitroso-varenicline. The FDA stated that *N*-nitroso-varenicline may be

associated with a potential increase in cancer risk in humans, but there is no immediate risk for patients. FDA stated that the benefits of stopping smoking would outweigh the cancer risks from use of the medication. However, FDA (2021e) also stated that the health care provider should consider other available treatment options and that they had determined that the recalled varenicline poses an unnecessary risk to patients.

- On the current FDA information site on nitrosamines, in the information section for health-care professionals, the FDA (2021c) states that they should continue to prescribe medications when clinically appropriate, even if they may contain low concentrations of nitrosamine impurities.

Zhejiang/Prinston valsartan products were reportedly sold in the United States for approximately 3 years, from 2015 to July 2018. Aurobindo's valsartan products were sold in the United States for approximately two years, in 2017–2019. Mylan's products were available for approximately six years (Valsartan HCTZ: September 2012 – December 2018; Valsartan: January 2015 – December 2018; and Amlodipine and Valsartan March 2015 – December 2018). Torrent's valsartan products were used during the following time periods: (1) Valsartan: January 2015 – July 2016; (2) Amlodipine Valsartan: March 2015 – September 2018; and (3) Amlodipine Valsartan HCTZ: June 2015 – September 2018. The valsartan product from Hetero Labs, Ltd., that reportedly contained NDMA/NDEA was sold during May and June of 2018. The recall of all amlodipine-valsartan products began 11/27/2018. Teva valsartan products that reportedly contained NDMA/NDEA were sold in the United States for less than four years – from September 2014 through November 2018 (valsartan – September 2014 through June 2018; valsartan/hctz – January 2015 through June 2018; amlodipine valsartan – March 2015 through November 2018; and amlodipine valsartan/hctz – December 2014 through November 2018).

It is my understanding that, in this matter, the plaintiffs and their experts are alleging the following claims:

1. That NDMA and NDEA are or should be considered human carcinogens.
2. That exposures to NDMA and/or NDEA are causally associated with various forms of cancer, including bladder, blood (leukemia, lymphoma, and multiple myeloma), breast, colorectal/intestinal, esophageal/pharyngeal, gastric, kidney, liver, lung, pancreatic, pharyngeal, prostate, and uterine cancers.[1]
3. That exposure to NDMA and/or NDEA from the use of valsartan products from one or more of the defendant's companies has caused plaintiffs to be at an "increased risk" of developing cancer from their reported exposures, or that they have already developed cancer.

As requested, I have reviewed and evaluated the materials provided to me regarding the above-mentioned matter to evaluate certain issues relating to NDMA and NDEA. Those issues relate to the toxicity and carcinogenicity of NDMA and NDEA; the regulatory

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1 Sources: Plaintiffs' Disclosure of Cancer Types; Dr. Etminan's report; Dr. Panigrahy's report.

treatment of NDMA and NDEA; the nature of regulatory assessment and classification of NDMA, NDEA, and chemicals in general; and the theoretical excess cancer risks from exposures to NDMA and NDEA from valsartan compared to the risks from endogenous and exogenous and nitrosamines from endogenous, as well as exogenous exposures; and the risks posed by daily exposures to other chemicals classified as carcinogens. Finally, I have considered the scientific issues surrounding the plaintiffs' claimed need for medical monitoring. My opinions on those matters are set forth in this report.

My opinions in this matter are based on the materials I have reviewed, my education, my experience in toxicology, my knowledge of the toxicity of the chemicals at issue, my understanding of the proper and well-accepted methods for assessing causation (e.g., including, but not limited to, consideration of exposure, dose, dose-response, temporality, alternative causes, and coherence). In the paragraphs below, I present the scientific background and the methods I used in forming my opinions, my opinions, and the bases for these opinions.

4 Background and Methods Used

Toxicology is the science that studies the adverse effects (toxicities) that chemical, physical, or biological agents (toxicants) might induce in biological systems. Much like medicine, toxicology is a multidisciplinary field of study, because it examines the physiological, pathological, biochemical, and molecular changes that various agents induce in organisms following interaction with some extra- or intra-cellular molecular entity. In fact, the study of the toxic effects of chemicals in toxicology differs little from the manner in which the beneficial or therapeutic effects of drugs are studied in pharmacology; the main difference is that a beneficial or therapeutic endpoint versus an undesirable or harmful endpoint is being investigated. Regardless of the types of toxicities that a chemical might induce, toxicologists perform two basic functions: (1) examine and characterize the specific set of adverse effects that a chemical agent is capable of causing (the hazard identification/characterization function), and (2) use dose-response relationships to assess the probability that these toxicities will or will not occur under specific conditions of exposure (the safety or risk assessment function).

Figure 1 below provides a basis for the classification of toxic effects according to site and degree of exposure. To cause tissue injury, a substance must come into contact with an exposed body surface, which may be the skin, the eye, or the lining membranes of the respiratory and gastrointestinal tracts. An adverse effect that occurs at the site of contact with the organism is referred to as a local effect or local toxicity (e.g., burning of the mucous membranes of eyes, nose, and throat after inhalation of a high concentration of an irritant). However, an adverse effect can result from absorption and distribution of a toxicant to a site distant from its entry point (i.e., the toxicant requires absorption and distribution within the organism to produce the toxic effect). This is known as a systemic effect or systemic toxicity. An example of this would be the adverse kidney or central nervous system effects resulting from chronic ingestion of sufficient doses of mercury. Systemic effects can be produced by the parent material that is absorbed, or by conversion products following absorption. The effects may be restricted to one organ or tissue system

or may manifest in multiple organs and tissues. Some materials may cause both local and systemic toxicity (Britt and James, 2017).

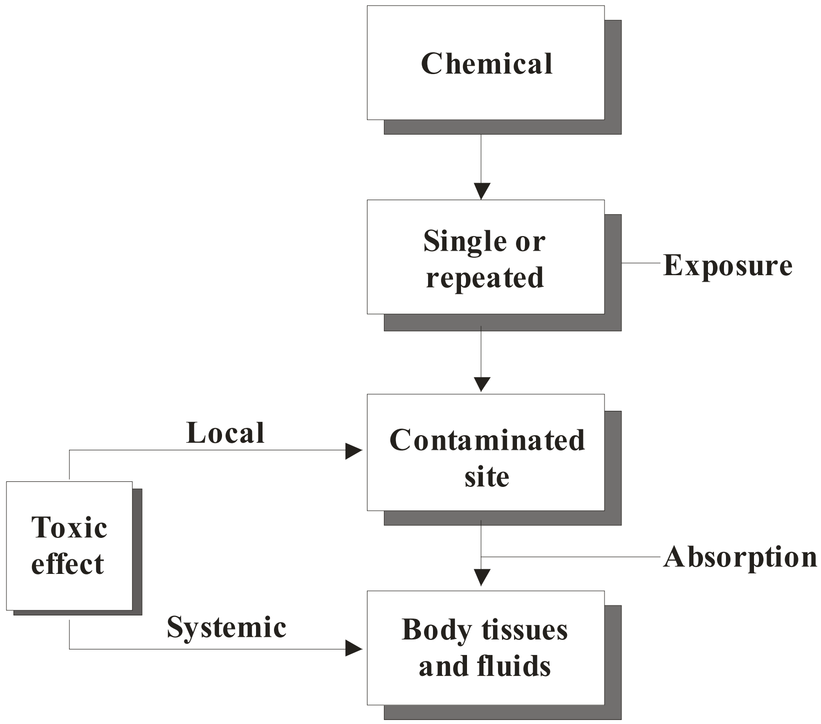

Figure 1. Schematic representation showing the basis for classification of toxic effects into either local or systemic, by single or repeated exposures

Some useful basic terms in toxicology are provided below:

- **Exposure** — A measure of the opportunity for contact with a chemical in one's environment. The presence of a chemical in an environmental medium of contact (e.g., in the air we breathe, the water we drink, on surfaces we touch, and in foods we might eat). Exposure levels are typically expressed in terms of the concentration of the chemical in the contact medium (e.g., as the ppm concentration in air or water).
- **Dose** — The total amount of a toxicant that an organism receives as the result of some exposure. The definition of dose typically refers to the applied dose, but different definitions and terms arise for the concept of dose as we move from the site of contact on the body to the amount absorbed and then distributed to the various tissues of the body.
- **Applied dose** — This is the total amount of the chemical that is directly applied to or has direct contact with those body surfaces that represent a portal of entry (via absorption) into the body. The applied dose can be higher than the absorbed dose, because all of the chemical does not necessarily cross the membranes or surfaces at the site of contact.

- **Acute toxicity** — An adverse or undesirable effect that is manifested within a relatively short time interval, ranging from almost immediately to within several days following exposure (or dosing). An example would be chemical asphyxiation from exposure to a high concentration of carbon monoxide (CO).
- **Chronic toxicity** — A permanent or lasting adverse effect that is manifested after exposure to a toxicant. An example would be the development of silicosis following a long-term exposure to silica in workplaces such as foundries.
- **Reversible toxicity** — An adverse or undesirable effect that can be reversed once exposure is stopped. Reversibility of toxicity depends on a number of factors, including the extent of exposure (time and amount of toxicant) and the ability of the affected tissue to repair or regenerate. An example includes hepatic toxicity from acute acetaminophen exposure and liver regeneration.
- **Delayed or latent toxicity** — An adverse or undesirable effect appearing long after the initiation and/or cessation of exposure to the toxicant. An example is cervical cancer during adulthood resulting from *in utero* exposure to diethylstilbestrol (DES).
- **Mechanism of action** — The necessary biological interactions by which a toxicant exerts its toxic effect on an organism. A simple example is CO asphyxiation due to the binding of CO to hemoglobin, thus preventing the transport of oxygen within the blood.
- **Toxicant** — Any substance that causes a harmful (or adverse) effect when in contact with a living organism at a sufficiently high concentration. Toxin—any toxicant produced by an organism (floral or faunal, including bacteria)—that is, naturally produced toxicants. An example would be the pyrethrins, which are natural pesticides produced by pyrethrum flowers (i.e., certain chrysanthemums) that serve as the model for the manmade insecticide class pyrethroids.
- **Potency** — A measure of the ability of a chemical to express its toxicity per unit of dose or dosage. The more potent a chemical is, the smaller the dosage needed to induce the toxicity it produces. In general terms, the less potent a chemical is, the safer it is, because the probability of achieving a dose sufficient to induce toxicity via a particular route of exposure is lessened. Similarly, more potent chemicals tend to be more dangerous, because it takes a smaller dose from an exposure to be able to induce toxicity.
- **Hazard** — The qualitative nature of the adverse or undesirable effect (i.e., the type of adverse effect or toxicity that the chemical produces) resulting from exposure to a particular toxicant or physical agent. For instance, asphyxiation is the hazard from acute exposures to CO. Cancer, liver toxicity, and immunotoxicity are other hazards (types of toxicities) that a chemical exposure might potentially present. A hazard typically refers to the kind(s) of toxic effect(s) the chemical can produce if the exposure/dose is sufficient.

- **Safety** — The measure or mathematical probability that a specific exposure situation or dose will not produce a toxic effect.
- **Risk** — As generally used in toxicology, the measure or probability that a specific exposure situation or dose will produce a toxic effect.
- **Risk assessment** — The process by which the potential (or probability of) adverse health effects of exposure are characterized. In risk assessment, a safe exposure concentration is extrapolated from the dose-response curve for an adverse effect produced by the chemical that is used to derive a safe exposure concentration. Alternatively, a risk assessment might determine the probability and/or acceptability of a toxicity occurring at a known or measured exposure level.

A fundamental principle of toxicology is that "the dose makes the poison." This principle was noted over 400 years ago by the Swiss philosopher and physician Paracelsus (1493–1541) when he stated (Gallo, 2008):

> *All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.*

This statement reflects the reality that the benefit or harm of every chemical exposure depends on the dose one receives. In toxicology and regulatory risk assessment, the importance and necessity of establishing and knowing the dose cannot be overstated.

A corollary to this basic principle is the fact that, regardless of the potency of the chemical, there is always a range of doses for which there is either no chance, or only an insignificantly small theoretical possibility, of an adverse effect occurring from that exposure. Exposures that occur within this range generate acceptably safe doses that do not raise public health concerns. In fact, the determination of the acceptably safe dose range for a chemical forms the very basis of all regulatory exposure guidelines. Emil Mrak emphasized these concepts when he stated (Casarett, 1975):

> *There are no harmless substances; there are only harmless ways of using substances.*

Without knowing the dose or the correct dose-response relationship, the risk of toxicity or safety cannot be evaluated. A simple graphic of Paracelsus's caution and how it applies to all substances is seen in Figure 2. This figure lists the lethal doses for three substances to which most or all adults have been exposed: water, beer, and salt. While one might find it surprising to think that a dose of something as simple and necessary to sustain life, like water, could be fatal, ingesting 15 quarts of water in a 24-hour period can be fatal. Typically, this toxicity is seen in individuals with a serious psychological disorder, but it was also recently seen in during a radio-station-sponsored contest to see who could drink and hold the most water to win a new gaming system. One of the participants unfortunately died from water intoxication on the day of the contest.

Figure 2. Acute lethal dose comparisons of three commonly used substances

An illustration of the statement made by Emil Mrak is shown in Figure 3, showing that the dose of aspirin increases as one moves through several different desirable target organ effects into those doses that are toxic to other target organs and, finally, lethality. So, as one can see, all chemicals are toxic at some dose and may cause harm if the exposure and dose are sufficient (e.g., even water and aspirin).

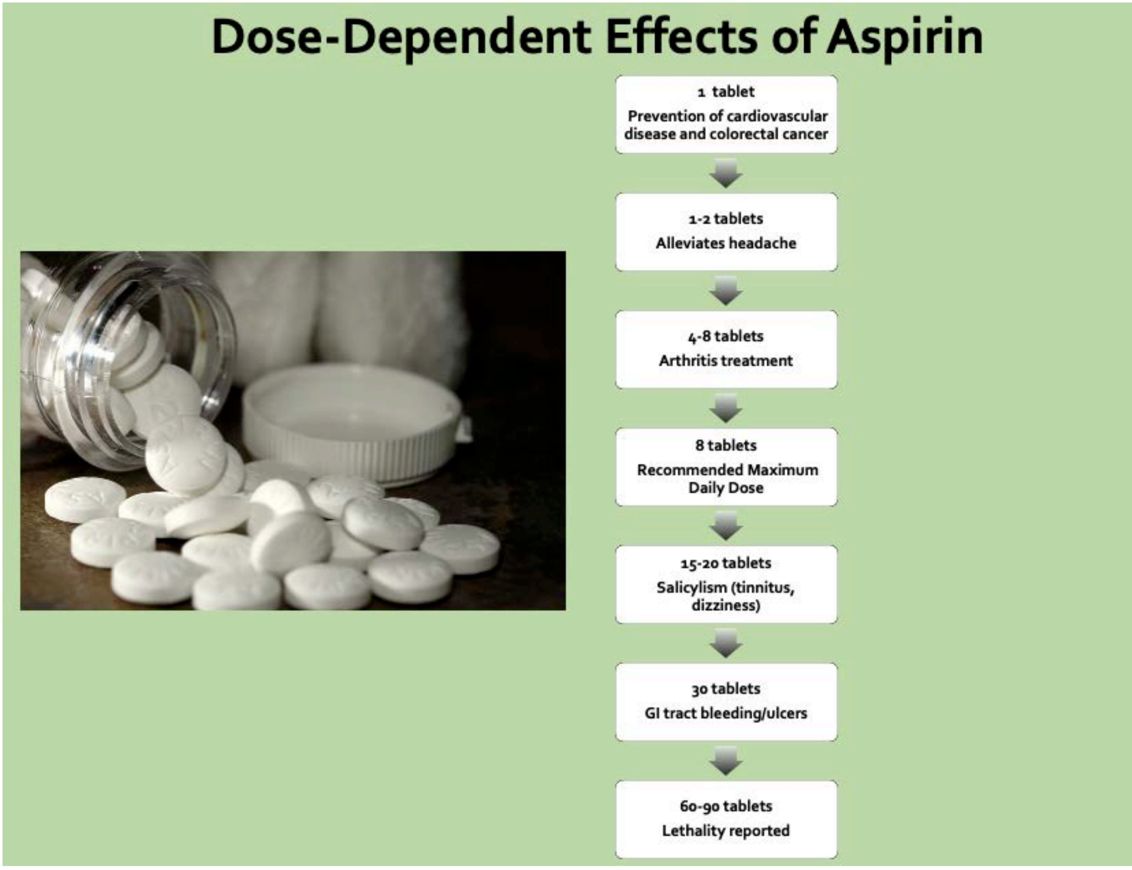

Figure 3. The dose-response curve for the therapeutic and potential adverse effects of aspirin

Part of toxicology involves evaluating the scientific literature on a compound and estimating safe human doses. Typically, the basis of this dose is the dose response and the threshold dose (e.g., a no-observed-adverse-effect level, or NOAEL), which can be defined as the dose below which no toxicity is observed or occurs. Thresholds can be seen for both noncancer and carcinogenic effects. Various types of dose-response curves are shown in Figure 4 below (James et al., 2015).

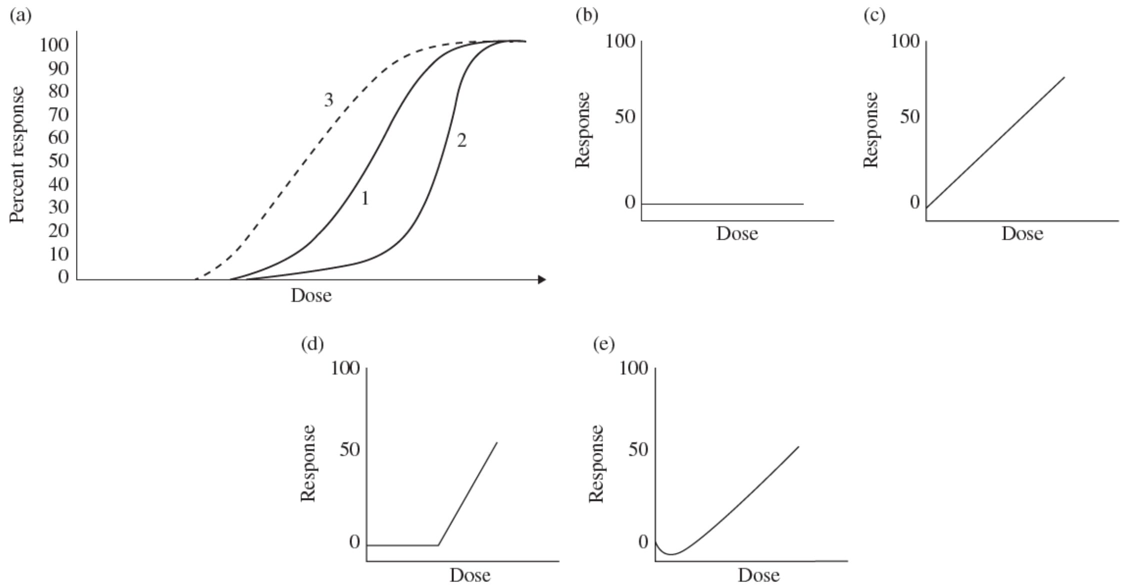

Figure 4. (a) A dose–response curve with log-linear (1), sublinear (2), and supralinear (3) shapes. (b) A dose–response curve where no effect is seen in the range of doses tested. (c) A graphical depiction of a linear, non-threshold type of dose–response curve; this shape is typically used for carcinogenic substances by regulatory agencies. (d) A representation of a nonlinear, threshold-dependent (commonly referred to as a "hockey stick"–shaped dose response). (e) The "J-shaped" dose-response curve seen with hormesis, a condition where low doses reduce toxicity or represent a beneficial effect that disappears as the dose increases and changes to a toxic response at higher doses. Dose-response curves for vitamins, hormones, and medicines frequently express this dose-response curve shape as the desired or beneficial effects are replaced by toxic effects at higher doses. Source: James (2015).

Regulatory bodies typically take a conservative approach in developing safe exposure levels for chemical-induced effects. They use the toxicity data for the chemical they are evaluating (e.g., an animal toxicity test) and use it to extrapolate to a corresponding safe dose in humans. Because all exposures that produce doses less than the threshold dose (or a NOAEL) should be devoid of toxicity, all exposure below these points are meant to represent safe exposure levels, even though these levels are not bright lines between safe and unsafe. However, when extrapolating from animal data, as must typically be done in toxicology, there is always some uncertainty as to how closely the animal dose–response data quantitatively and qualitatively mimic the actual human dose-response curve. As a conservative approach then, safety/uncertainty factors are selected, and the NOAEL/threshold dose is divided by a total safety/uncertainty factor from a combination of different uncertainty factors that each reflects the uncertainty of the dose-response data being used in the extrapolation (see Figure 5).

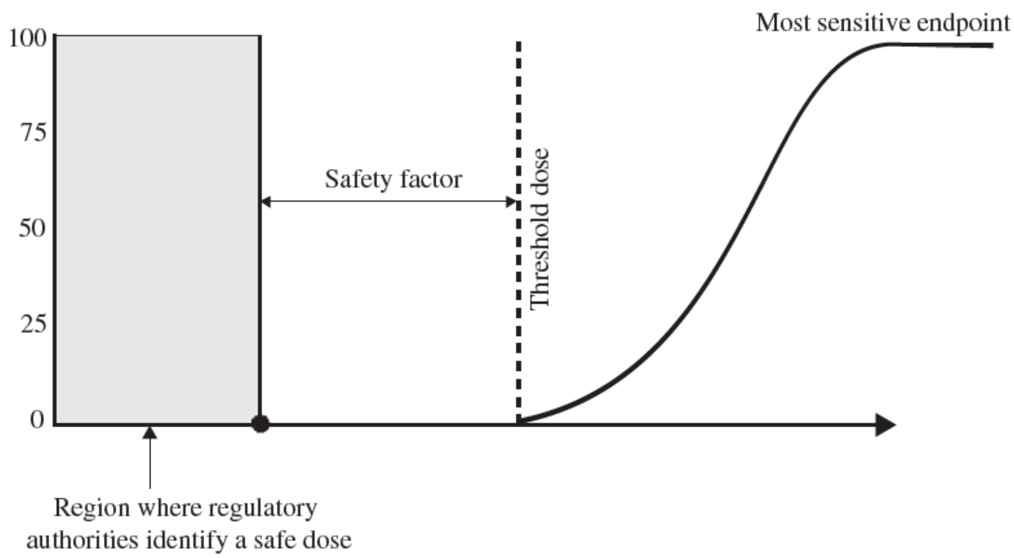

Figure 5. Graphical representation showing how the regulatory community develops safe exposure levels for chemical-induced toxicities. Beginning at a dose where the adverse effect is not likely to be induced (i.e., the threshold or NOAEL dose), the allowable dosage rate is then reduced further by the adoption of safety (uncertainty) factors based on the strength of the available evidence. Reductions by a factor of 10-fold are typically adopted based on the presence of characteristics of the dose-response curve under consideration, such as the following: (1) use of animal (nonhuman) data, (2) use of less-than-chronic exposure duration data, and (3) limited toxicity testing and similar characteristics that contribute to the uncertainty of the extrapolation being made. (For carcinogens, we now use benchmark doses [BMDs] that incorporate large uncertainty factors.)

After accounting for the potential uncertainty associated with the threshold/NOAEL dose, the final dose selected is considered to be a "safe dosage" that can be used in the development of human exposure guidelines for that chemical (Figure 5). As can be seen in Figure 5, the net effect of dividing the threshold or NOAEL dose by some total safety/uncertainty factor is to select a substantially lower dose from the no-effect region of the dose–response curve. Species-related differences that should be considered in predicting safe or unsafe human exposure situations are discussed later in this report.

Concerning the setting of safe doses for impurities in drug substances and drug products, various guidance documents have been published. The Pharmaceutical Research and Manufacturers of America published a position paper in 2006 titled, *A Rationale for Determining, Testing and Controlling Specific Impurities in Pharmaceuticals*. At about the same time, the European Medicines Agency (EMA) developed related guidelines, *Guidelines on Limits of Genotoxic Impurities*, published in 2010 and 2012. The FDA published their draft guidance—*Genotoxic and Carcinogenic Impurities in Drug*

Substances and Products: Recommended Approaches—in 2008 (Bobst and Sukmar, 2019).

The International Council for Harmonisation (ICH) M7(R1) guidance, also known as the "M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk: Guidance for Industry" (FDA, 2018) was introduced in 2014 and updated in 2017 and again in 2018 (FDA, 2018). This document provides a framework by which to assess the carcinogenic risk of mutagenic and carcinogenic pharmaceutical impurities. The default approach for mutagenic carcinogens is to use linear low-dose (non-threshold) extrapolation from cancer dose-response data. An example of a dose used in such an extrapolation is the dose that results in tumors in 50% of the test animals (or TD_{50}). The TD_{50} values for many compounds can be obtained from studies that are available in the Carcinogenicity Potency Database (CPDB, 2004) which is now maintained as the Lhasa Carcinogenicity Database.[2] The TD_{50} value for a specific chemical is used to calculate a lifetime acceptable intake (AI) (e.g., by FDA or EMA). As noted by Johnson et al. (2021), these TD_{50}-based AIs are very conservative for human risk assessment. Other safe limits or doses have also been calculated for drug impurities, including AIs based on alternative points of departure (PODs), such as benchmark doses (BMDs), permitted daily exposures (PDEs), virtually safe doses (VSDs), and doses based on the less-than-lifetime (LTL) acceptable intake (Snodin and Elder, 2019; Bercu et al., 2021). These are defined briefly as follows (Bercu et al., 2021):

- BMD — The lower confidence limit of the dose the causes a specified measure or changes of a biological effect.
- PDE — A substance-specific dose that is not likely to cause adverse effects when a person is exposed at or below this dose every day for their lifetime.
- LTL acceptable intake — An acceptable intake that can be used in instances where a medication (that also contains an impurity) is administered for less than an individual's entire lifetime. The acceptable cumulative lifetime dose is distributed uniformly over the total number of days an individual is exposed during the "less-than-lifetime" exposure. This concept is related to a time and dose relationship in toxicology called Haber's law, which is $C \times T = k$, where C is concentration, T is time, and k is a constant. The LTL exposures for carcinogens have been used since the mid-1980s.
- VSD — A dose obtained by linear extrapolation to a dose, or range of doses, that pose a theoretical risk(s) whose magnitude is acceptably low from a public health standpoint. An excess risk of 1×10^{-6} is considered acceptable, and the related dose is called "virtually safe."

[2] Link: https://www.lhasalimited.org/products/lhasa-carcinogenicity-database.htm.

5 My Opinions

5.1 Opinions

5.1.1 Opinion #1 — The overall body of scientific information shows no evidence of causation for NDMA or NDEA for cancer in humans. Furthermore, the plaintiffs' alleged exposure to NDMA and/or NDEA contained in valsartan API and/or finished dose does not increase cancer risk above the background risk incurred from other exposures to NDMA, NDEA, and other nitrosamines, or over the risk from other commonplace exposures to carcinogens.

To say that a chemical exposure creates a risk of a future disease necessarily implies that the exposure at issue is capable of causing the disease. An accepted method exists by which to assess causation in toxicology (e.g., USDHEW, 1964; Hill, 1965; Evans, 1976; Hackney and Linn, 1979; Monson, 1980; Doll, 1984; Sackett, 1985; Gehlbach, 1988; Guidotti and Goldsmith, 1986; Susser, 1977, 1986, 1991; Hennekens and Buring, 1987; Sacks and Schenker, 1990; Mausner and Kramer, 1985; Hernberg, 1992; Sullivan, 1992; Eisen and Wegman, 1995; Faustman and Omenn, 1996; Rothman and Greenland, 1998; Guzelian et al., 2005; NAS, 2006; Dickersin et al., 2007; Valerio, 2008; FDA, 2009; James et al., 2015; Wikoff and Britt, 2016).

After evaluating the allegations in this case and applying the appropriate methods, I conclude that the scientific evidence does not support the plaintiffs' allegations that NDMA or NDEA contained in valsartan API and/or finished dose cause the alleged cancers. In addition, I find that the calculated excess theoretical cancer risks from their reported exposure to NDMA and/or NDEA from valsartan API and/or finished dose show no increased risk compared to their risks from background/endogenous exposures to potential or known carcinogens during the course of everyday life. We all incur such exposures, which are far lower than the actual background risk of cancer that all individuals have (see below for more discussion). In addition, alternative etiologies (risk factors) will predominate as likely causes for any cancer identified.

5.1.1.1 Animal Data

NDMA and NDEA have been reported to cause tumors in several different species of test animals, at various tissue sites, via different exposure routes (e.g., see IARC, 1978, 1987; Peto et al., 1991a,b; WHO, 2002; NTP, 2016). NDMA treatment has been shown to produce different tumors among the various species tested, depending on treatment method (e.g., oral, inhalation, etc.). For example, oral administration of NDMA has been reported to result in liver tumors in mice, rats, hamsters, and guinea pigs; kidney tumors in rats and mice; blood-vessel tumors in mice, rats, and hamsters; and lung tumors in mice. Inhalation exposure is reported to cause liver and lung tumors in mice, kidney tumors in rats and mice, and nasal-cavity tumors in rats. Subcutaneous exposure has been reported to cause liver tumors in hamsters and newborn mice and rats, lung tumors in mice, blood-vessel tumors in mice and hamsters, and nasal-cavity tumors in hamsters. Intraperitoneal injection results in liver and lung tumors in adult and newborn mice, kidney tumors in rats and mice, blood-

vessel tumors in mice, and nasal-cavity tumors in rats (NTP, 2016). Intramuscular injection has been stated to result in liver tumors in rats. In some animal studies, short-term or single-dose treatments with NDMA have resulted in kidney tumors in rats (i.e., 100–500 mg/kg in the diet, or up to 30 mg/kg-bw; IARC, 1978).

NDEA has also been reported to cause tumors in various species of experimental animals, at different tissue sites, by various exposure routes. Oral exposure to NDEA has been reported to cause benign and malignant liver tumors in mice, rats, hamsters, guinea pigs, rabbits, dogs, and pigs; kidney tumors in pigs; upper-digestive-tract tumors in mice, rats, and hamsters; and lung and upper-respiratory-tract tumors in mice, rats, hamsters, dogs, and pigs. Inhalation exposure has been associated with liver tumors in rats, and tumors of the trachea, bronchi, and lungs in hamsters. Intraperitoneal exposure has caused liver tumors in mice, rats, and hamsters; lung tumors in mice; and respiratory-tract tumors in hamsters and monkeys. Subcutaneous injection has been reported to cause liver tumors in hamsters, guinea pigs, gerbils, and hedgehogs, and respiratory-tract tumors in adult and newborn mice and hamsters, in pregnant hamsters, and in adult guinea pigs, gerbils, and hedgehogs. Intravenous injection has been associated with nasal-cavity tumors in gerbils and kidney tumors in rats. Dermal exposure has been associated with nasal-cavity tumors in mice and hamsters. Rectal exposure has caused liver tumors in rats. Prenatal exposure caused benign lung tumors in mice and hamsters, kidney tumors in rats, and tumors of the upper digestive tract in mice (NTP, 2016).

On the other hand, studies have shown that carcinogenic responses in animals require administration of relatively high doses, and a reduction in the lifetime dose by as little as one-fourth or one-eighth of the cancer-causing dose fails to induce cancer in the responsive animal species. Moreover, the doses used to test chemicals for carcinogenic activity are so high that, if all the chemicals in our living environment (i.e., drugs, natural products, synthetic chemicals) were tested at similar levels under standard testing regimens, we would expect 50% of them to induce tumors in animals and, thus, to be classified as "probable carcinogens."

5.1.1.2 Epidemiological Data on NDMA-Containing Medications

Below is a summary of recent epidemiological studies that have been conducted on NDMA-containing medications. Overall, these studies do not show a causal association between exposure to NDMA or NDEA from the use of valsartan and the development of any type of cancer in humans. [I note that other defense experts in this case will be addressing the epidemiological studies of NDMA/NDEA-exposed individuals in more detail.]

- Pottegård et al. (2019) conducted a cohort study of 5,150 Danish patients who had no history of cancer to assess the cancer risk associated with exposure to NDMA from valsartan products. Subjects were selected from nationwide Danish healthcare registries who were 40 years and older and had begun using valsartan between January 1, 2012, and June 30, 2017. Patients were followed for one year after entering the cohort until developing cancer, dying, or migrating, or until the end of the study (June 30, 2018). Each individual's

exposures to NDMA (ever exposed and categories based on cumulative valsartan exposure) was determined. The median follow-up time was 4.6 years (interquartile range 2.0–5.5 years). There were 104 cancer outcomes among unexposed individuals and 198 among NDMA-exposed individuals, representing no significant increase in overall cancer (adjusted hazard ratio of HR = 1.09, 95% CI 0.85–1.41), and no dose-response was seen (p = 0.07). For individual cancer outcomes, no significantly increased HRs were reported for any individual cancer types evaluated (i.e., colorectal, uterine, pancreas, lung, melanoma, breast, prostate, kidney, or bladder). Thus, the findings of this study indicate that individuals who ingested valsartan containing NDMA were not at significantly increased risk of developing cancer overall, nor of developing any of the cancers investigated during the time period evaluated. The authors noted that no liver cancer events were seen among NDMA-exposed subjects and stated, "A marked increased risk of liver cancer associated with NDMA exposure thus seems unlikely." Overall, the authors concluded that their study showed no evidence of a marked increase in short-term overall cancer risk.

- Al-Kindi and Oliveira (2019) investigated trends in ARB-associated neoplasm adverse events (AEs) that were reported to FDA in their Adverse Events Reporting System (FAERS). They evaluated trends in AE reporting associated with valsartan (and other ARBs) between January 1, 2017, and December 31, 2018, and compared percentages of neoplasms using AEs by drug type (i.e., valsartan vs. other ARBs: losartan, candesartan, irbesartan, olmesartan, telmisartan). The study found that, since 2017, a total of 11,112 AEs had been reported (5,151 valsartan, 5,961 other ARBs), including 920 (8.7%) neoplasms (14.7% valsartan; 3.6% other ARBs). The number of AEs increased significantly more for valsartan (1,117 in 2018 Q1–Q2 to 2,671 in 2018 Q3–Q4) compared with other ARBs (1,634 in 2018 Q1–Q2 to 2,322 in 2018 Q3–Q4). The percentage of all reported AEs (valsartan to other ARBs) increased from 5.3% pre-recall to 23.4% post-recall. A monthly analysis showed an increase in reporting odds ratio in July 2018, continuing through August and September, and decreasing in October through December. The authors describe this as an *"...an abrupt and <u>biologically implausible</u> rise in valsartan-associated neoplasms in the third quarter of 2018, after a drug recall that attracted extensive national media coverage"* (emphasis added). They note that AE reports have shortcomings that include inaccuracy, being voluntary, and having delayed reporting. The authors commented on the biologically implausibility and lack of temporal relationship:

> *Although consumer reporting appeared to be the most susceptible to the widely covered recall, healthcare providers were also influenced. Interestingly, the duration of this effect was transient, as most cancer AEs were reported early after the recall and decreased over time, remaining above baseline. In a similar analysis of the FDA Manufacturer and User Facility Device Experience database, cardiovascular device recalls were also associated with increased reporting of AEs but differently, those preceded the recall, and persisted for a few months. In conclusion, after the widely covered*

> *valsartan recall in 2018, we found a steep and transient rise in reporting of ARB-associated cancers, which we think to be biologically implausible. This observed phenomenon was likely associated with public alarm and fueled mainly by consumer and lay reporting.*

- In an observational population-based cohort study, Yoon et al. (2021) evaluated the risk of various cancers following the use of NDMA-containing ranitidine products in South Korea. Using the Health Insurance Review and Assessment databases, a cohort of ranitidine users were enrolled in the study, along with a group of controls (users of famotidine, another H_2-receptor agonist, in which no NDMA had been detected). The cohort comprised individuals who had been prescribed ranitidine between January 2009 and December 2011, with patients prescribed famotidine during the same period being used as controls. The groups evaluated consisted of a 4:1 matched cohort of 40,488 ranitidine users and 10,122 famotidine users (controls). The HR for overall cancer rate was less than expected (HR = 0.99, 95% CI 0.91–1.07) or was withing the cancer rate for 11 individual cancer types between groups (i.e., liver, colorectal, biliary, stomach, lung, prostate, kidney, bladder, uterine, breast, or thyroid cancer). For five of the eleven individual cancers (liver, colorectal, lung, kidney, and breast), the HRs were less than expected (i.e., HR less than unity).
- Iwagami et al. (2021) conducted a study of the risk of cancer in association with ranitidine and nizatidine compared to other H_2-blockers using the Japan Medical Data Center Claims Database. Using data for the time period January 2005 to August 2018, 113,743 new users of ranitidine/nizatidine were identified from the database, along with 503,982 new users of other H_2-blockers. The median age was 41.2 years (interquartile range 31.7–51.1 years), and the median follow-up was 2.3 years (range 0.9–4.2 years). The adjusted HR for cancer was not significantly elevated (HR = 1.02, 95% CI 0.98–1.07). Similar results were seen when analyzed by individual cancer sites (i.e., breast, colorectal, and gastric cancer) and follow-up length. The adjusted HRs were not significantly associated with cumulative dose and decreased with increasing cumulative dose—i.e., 1.03 (0.98–1.08) from 1 to 180 defined daily doses (DDDs), 1.00 (0.73–1.39) from 181 to 365 DDDs, 0.95 (0.61–1.48) from 366 to 730 DDDs, and 0.83 (0.45–1.55) at >730 DDDs.
- Gomm et al. (2021) investigated the risk of cancer from the use of NDMA-containing valsartan in a longitudinal cohort study using the German Health Insurance Data. The cohort comprised patients over the age of 40 years who had filled at least one valsartan prescription between January 1, 2012, and December 31, 2017. In all, a total of 780,871 individuals had filled a valsartan prescription. The final study group was 409,183 classified as ever exposed, and 371,688 who were never exposed to NDMA- containing valsartan. The median person-times were 3.1 years (standard deviation 1.5 years, interquartile range 2–4.75 years). No significant increase in overall cancer was found (adjusted HR = 1.01, 95% CI 0.99–1.03). Using manufacturers' information on packages of valsartan drug products sold, authors were able to classify the filled

prescriptions into different degrees of likelihood of nitrosamine impurity (i.e., from possibly to probably). The authors reported a "slightly" significantly increase in hepatic cancer among individuals using valsartan (adjusted HR = 1.16, 95% CI 1.03–1.31), but not for the other cancers evaluated (i.e., bladder, breast, colorectal, kidney, lung, malignant melanoma, pancreatic, prostate, and uterine cancer). Authors noted that no dose-dependent effect on the liver cancer risk was seen for higher exposure to potentially NDMA- containing valsartan. When evaluating risk based on 3-year long-term use of potentially NDMA-containing valsartan, there was a decreased sample size (75,112 patients, 130 liver cancer cases), but there was no significant association with liver cancer (adjusted HR = 1.22, 95% CI 0.80–1.89). The authors noted that they were not able to adjust for risk factors for cancer, such as smoking habits, nutritional habits, and genetic predisposition.

5.1.1.3 Summary

While NDMA and NDEA have been found to be carcinogenic in several animal species, they are not considered to be known human carcinogens by regulatory and scientific bodies (e.g., EPA, 1987a,b; IARC, 1978, 1987; OEHHA, 2006; NTP, 2016; EMA 2020a). For example, EMA (2020a) evaluated the human evidence for nitrosamines and concluded, "Epidemiological studies are not yet providing convincing evidence for a quantification of the carcinogenic potential of Nitrosamines in humans." In addition, while NDMA and NDEA have been reported to cause tumors in various target organs in animal species, EMA (2019) notes the following areas of uncertainty where humans are concerned (emphasis added):

> *Target organ(s) of NDMA and NDEA in <u>humans are currently unknown</u>. In animal experiments across species the primary target organ is liver. Additionally, tumours were observed in oesophagus, kidney, vasculature system, gastrointestinal tract and lung with either NDMA and/or NDEA. However, <u>extrapolation to potential target organs for carcinogenicity in humans is highly uncertain</u>.*

Another agency that has assessed NDMA, the state of California's Office of Environmental Health Hazard Assessment (OEHHA, 2006), for its public health goal (PHG) in drinking water, has also noted the lack of conclusive evidence for carcinogenicity of NDMA in humans:

> *<u>Hazard Identification</u> - There is overwhelming evidence that exposure to NDMA resulted in increased incidence of cancer in animals. An increase in tumors associated with NDMA exposure has been observed in a variety of animal species, in both males and females, by both oral and inhalation exposure routes, in immature and mature animals, and using a number of experimental protocols. Studies of human exposure are much more limited and are suggestive but certainly not conclusive that human exposure to NDMA results in an increase in cancer.*

Based on a review of the scientific evidence on the chemicals at issue in this case, there is no support for a causal association between exposure to NDMA and NDEA and cancer in humans. This conclusion is based on a review of the epidemiological evidence of individuals exposed to NDMA contained in medications and the conclusions of various regulatory and scientific agencies.

5.1.2 Opinion #2 —The FDA and EMA Interim AIs for NDMA and NDEA involve a number of conservative assumptions and safety factors, such that the values derived cannot be viewed as the dividing line between "safe" and "unsafe" concentrations. Other safe doses for NDMA and NDEA, based on up-to-date risk assessment methodology have been derived and provide more reliable values.

5.1.2.1 FDA's Derivation of AIs for NDMA and NDEA

To propose an "acceptably safe" dose of NDMA and NDEA for valsartan, the EMA/FDA relied on data from a lifetime bioassay, a study conducted where test animals (typically rodents) are exposed to a chemical over their lifetime and then examined for tumor development. In developing the acceptable intakes (AIs) for NDMA and NDEA [which are classified as probable, not known, human carcinogens (IARC, 1987)], the EMA/FDA used data from the Carcinogenic Potency Database (CPDB)[3]. An AI is defined as an acceptable intake level compound that approximates a 1:100,000 cancer risk after 70 years of exposure (FDA, 2019a). The AI for NDMA was calculated based on rodent carcinogenicity potency data known as the TD_{50}, defined as the daily dose that resulted in a 50% tumor incidence (or 1:2) in the test animals. The linear extrapolation to a probability of 1 in 100,000 (FDA's and EMA's accepted lifetime risk level) was determined by dividing the TD_{50} by 50,000. In other words, to determine the dose that would cause tumors in 1 in 100,000 animals, the TD_{50} was divided by 50,000 (FDA, 2018). The AI (in mg/day) was calculated using a human body weight of 50 kg. Linear extrapolation from the TD_{50} value was considered appropriate by EMA to derive the AI (for M7 Class 1 impurities with no established threshold mechanism). The TD_{50}s that were available for NDMA in the CPDB were 0.096 mg/kg/day for the rat[4] (based on the oral exposure to NDMA by Peto et al., 1991) and 0.189 mg/kg/day for the mouse (the source of this value was not provided). The most conservative (i.e., lower) TD_{50} value was used to calculate the AI. For the NDMA AI (i.e., the intake associated with a 1 in 100,000 cancer risk over 70 years of exposure), the TD_{50} of 0.096 mg/kg/day was divided by 50,000, then multiplied by 50 kg body weight. The resulting lifetime NDMA AI was calculated to be 0.0000959 mg/day or 96 ng/day (EMA,

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3 At the time the EMA conducted its risk assessment on NDMA and NDEA, the CPDB contained 6,540 long-term animal cancer bioassays on 1,547 chemicals (EMA, 2020a). The CPBD has since been transferred to the Lhasa Carcinogenicity Database, which now contains 7,745 studies on 1,726 chemicals (Lhasa, 2021). The previous version of the CPBD can be downloaded (in bulk) from the NIH at https://www.nlm.nih.gov/databases/download/cpdb.html.

4 The updated Lhasa TD_{50} for the rat is 0.177 mg/kg/day for NDMA, with no change for the mouse.

2019; FDA, 2020, 2021b) (see equation below). Per the EMA and FDA, the 96 ng NDMA/day AI limit corresponds to 0.3 ppm in a 320 mg tablet of valsartan.[5]

$$\frac{\frac{0.096\frac{mg}{kg}}{day}(TD50)x\ 50\ kg\ x\ 10^6\ (conversion\ rate\ mg\ to\ ng)}{50{,}000} = 96\frac{ng}{day}NDMA$$

Importantly, as noted by the EMA (2019), the AIs of 96 ng/day for NDMA corresponds to *theoretical*, not actual, cancer risks. EMA (2020a) comments on the problems extrapolating results of Peto et al. (1991a), which was used as the basis for the NDMA AI, to humans:

> *According to the Ad-hoc expert group there also seem to be significant doubts among experts on whether this linearity for some tumours in rodents is transferable to humans. This is also stated by Peto et al. (1991a) in their publication: "This provides us with what is probably a reasonably reliable estimate (despite the practical impossibility of direct confirmation) of the effects of ppb nitrosamine concentrations on rats under these experimental circumstances, but it does not provide reliable information as the effects of ppb nitrosamine concentrations on humans, and it would be a serious distortion of these experimental results to suggest otherwise."*

Similar to NDMA, an AI for NDEA was derived after considering the TD_{50}s for NDEA available in the CPDB. Of several TD_{50}s listed for the rat, cynomolgus monkey, and bush babies, the TD_{50} of 0.0265 mg/kg/day was chosen based on data for the rat (liver tumors were reported for animals tested; other tumor types were also reported in male rats) (EMA, 2019). The lifetime AI was calculated by FDA (2019b) to be 26.5 ng/day (or 0.083 ppm in a 320 mg/day tablet[6]) (see equation below).

$$\frac{\frac{0.0265\frac{mg}{kg}}{day}(TD50)x\ 50\ kg\ x\ 10^6\ (conversion\ rate\ mg\ to\ ng)}{50{,}000} = 26.5\frac{ng}{day}NDEA$$

In their assessment of exposure to NDMA from use of valsartan, the FDA (2019a) estimated there would be one additional excess cancer per 8,000 individuals (or $1.25x10^{-4}$) for patients who took valsartan at the "highest valsartan dose (320 mg/day) containing NDMA from the recalled batches daily for four years." The FDA (2019a) also stated for the NDEA impurity in valsartan, there would be an additional 1 in 18,000 cases of cancer (or 5.6×10^{-5}) if individuals took valsartan at the highest dose for four years.

In addition to NDMA and NDEA, FDA derived limits for several other nitrosamines, noting that the AI limits are applicable only if a drug contains a single nitrosamine. A single

5 The conversion of the AI into ppm depends on the product and is based on the drug's maximum daily dose (MDD) as reflected in the drug label; i.e., ppm = AI (ng) ÷ MDD (mg). For example, for NDMA in a product with 320 mg MDD, the acceptable intake in ppm is 0.3 ppm (96 ng ÷ 320 mg = 0.3 ppm) (FDA, 2021b).

6 I.e., [ppm = AI (ng) ÷ MDD (mg)] or 26.5 ng ÷ 320 mg = 0.083 ppm (FDA, 2021b).

nitrosamine compound can be present up to its AI, with an AI of ≤26.5 ng/day if there is more than one nitrosamine impurity identified (FDA, 2021d).

Using Haber's rule, the EMA (2019) calculated cumulative doses for NDMA from valsartan over the potential exposure period. EMA (2019) describes their procedure and Haber's rule:

> *According to the Haber's rule, a fundamental principle in toxicology generally accepted to be used for mutagenic carcinogens and therefore considered appropriate for NDMA, the total dose taken over time (dose x time) produces a fixed level of effect, thus, determining the risk associated with the exposure. Applying this very conservative principle, the cumulated dose acceptable for lifetime is then the AI multiplied by the days of a lifetime (70 years is generally accepted for this) of 25,550 days.*

In the sections below, I will calculate the excess theoretical cancer risks for the plaintiffs for NDMA and NDEA associated with the use of valsartan.

5.1.3 Opinion #3 – The plaintiffs' estimated excess theoretical cancer risk from their reported exposure to NDMA and/or NDEA from valsartan products shows no increase over the excess cancer risk from exposure to endogenous NDMA and the background risk of developing cancer experienced by everyone.

Excess theoretical cancer risk calculations for NMDA and NDEA, similar to the ones calculated by the FDA/EMA, were calculated using analytical data for NDMA and NDEA from Prinston, Aurobindo, Mylan Pharmaceuticals, Teva Pharmaceuticals, and Torrent Pharmaceuticals based on the data provided by the FDA on their site—*Laboratory Analysis of Valsartan Products* (FDA, 2019b).[7] FDA (2019b) presents data for NDMA and NDEA as the range of averages of NDMA and NDEA [in micrograms (µg) per tablet] by product for each pharmaceutical company. Tables 1 and 2 below show the lowest and maximum NDMA and NDEA values (in ng) detected for each company (for any valsartan-containing product). The lifetime average daily dose (LADD) calculation represents a worst-case dose based on the data provided by FDA (2019b), because it assumes that NDMA/NDEA-containing valsartan was taken the entire time it was available to the public, when in reality, a patient may have taken medication from an affected batch for only a single fill or over the course of a few months. Using the LADD, excess theoretical cancer risks for NDMA and NDEA were calculated based on FDA's risk values (i.e., a lifetime exposure to 96 ng NDMA or 26.5 ng NDEA representing a 1 in 100,00 cancer risk). The excess cancer risks (based on the low-end and maximum levels) of NDMA range from 2.98×10^{-9} to 9.85×10^{-5}. The cancer risks for NDEA (for the low-end and maximum levels) range from 0 (no NDMA detected so no excess risk) to 2.12×10^{-5}. The combined NDMA + NDEA low average and maximum average excess cancer risks range from 2.98×10^{-9} to 1.15×10^{-4}, respectively (Table 3). Even if a patient would have taken medications from one or more manufacturers at different time points, it is not likely that their excess

[7] https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products.

cancer risk would have resulted in a significantly increased risk above background. In addition, all these theoretical excess cancer risks are within the 10^{-4} to 10^{-6} acceptable risk range used by many regulatory bodies.

For example, the EMA (2019) calculated example lifetime excess theoretical cancer risks from a "worst-case" NDMA/NDEA exposure scenario from co-exposure to valsartan. In this risk calculation, EMA (2019) considered co-exposure to NDMA (for 6 years) and NDEA (for 4 years)] and compared the risks to background cancer risk. The resulting combined cancer risk for NDMA+NDEA was 2.95 x 10^{-4}. Note that this risk level is higher than the risk level calculated for the plaintiffs in this matter. This EMA calculated combined risk value was stated by EMA (2019) to be "theoretical" and "very low" compared to background cancer risks faced by the European Union population in general:

> *For patients exposed for 6 years to NDMA-contaminated valsartan assuming a 1:1 transfer of the impurity from API to finished product and a mean NDMA content of 24.1 µg* [24,100 ng] *in a 320 mg tablet, the theoretical excess risk of cancer during lifetime is calculated to be 21.5 in 100,000* [2.15 x 10^{-4}]. *This is approximately 0.02%. For patients exposed for 4 years to NDEA-contaminated valsartan assuming a 1:1 transfer of the impurity from API to finished product and a mean NDEA content of 3.7 µg* [3,700 ng] *in a 320 mg tablet, this theoretical excess risk is calculated to be 8 in 100,000 (0.08%)* [8 x 10^{-5}]. *The excess risk in patients co-exposed to both NDMA and NDEA for 4 years and NDMA alone for 2 years is calculated to be 29.5 in 100,000 or 0.03%.* [3 x 10^{-4}]
>
> *Compared to the overall risk of cancer during lifetime for the EU population (e.g.in Germany reportedly 50.3 % in men and 43.5 % in women; in Italy 62% in men and 59% in women) the theoretical additional risk due to the highest levels reported of NDMA/NDEA in some valsartan batches is considered very low.*

Also, as will be discussed later, these excess risks are lower than and/or similar to excess cancer risks we all incur from chemicals to which we are exposed on a daily basis—e.g., in the foods we eat, air we breathe, water we drink, lifestyle (exposure to tobacco smoke), and medications or medical treatments we receive. These theoretical excess cancer risks from NDMA and NDEA are far lower than the actual risk of developing cancer in a lifetime.

Table 1. Low and maximum average NDMA-related valsartan doses and excess cancer risks based on data from various sources*

	Low Average Concentration		Maximum Average Concentration	
Company**	**LADD (ng)**	**Excess Cancer Risk**	**LADD (ng)**	**Excess Cancer Risk**
Prinston	564.86	5.88×10^{-5}	865.29	9.01×10^{-5}
Aurobindo	0.03**	2.98×10^{-9}	–	–
Hetero	0.77	8.07×10^{-8}	1.03	1.08×10^{-7}
Mylan	0.09**	8.93×10^{-9}	–	–
Teva	0.06	5.95×10^{-9}	945.71	9.85×10^{-5}
Torrent	19.29	2.01×10^{-6}	494.14	5.15×10^{-5}

LADD: Lifetime average daily dose; – : Only <LOD was reported, so no maximum LADD or cancer risk were calculated.

*Data on NDMA and NDEA levels used in calculations were from FDA's Website – "Laboratory Analysis of Valsartan Products" (FDA, 2019b).

**Duration of exposure: Prinston, 3 years; Aurobindo, 2 years; Mylan, 6 years: Hetero, two months; Teva, 4 years; and Torrent, 3 years.

**1/2 of the LOD value was used.

Table 2. Low and maximum average NDEA-related valsartan doses and excess cancer risks based on data from various sources*

	Lowest Average Level		Maximum Average Level	
Company**	**LADD (ng)**	**Excess Cancer Risk**	**LADD (ng)**	**Excess Cancer Risk**
Prinston	0.13***	4.85×10^{-8}	–	–
Aurobindo	0	0	5.43	2.05×10^{-6}
Hetero	0.1***	2.66×10^{-9}	–	–
Mylan	3.43	1.29×10^{-6}	32.57****	1.23×10^{-5}
Teva	0	0	44.00	1.66×10^{-5}
Torrent	0.13***	4.85×10^{-8}	56.14	2.12×10^{-5}

*Data on NDMA and NDEA levels used in calculations were from FDA's Website – "Laboratory Analysis of Valsartan Products" (FDA, 2019b).

**Duration of exposure: Prinston, 3 years; Aurobindo, 2 years; Mylan, 6 years: Hetero, two months; Teva, 4 years; and Torrent, 3 years.

***1/2 of the LOD value was used.

**** This figure is based on data published by the FDA. I am aware that Mylan also compiled additional testing data (see MYLAN-MDL2875-00895544). I have reviewed these data, and they do not alter my opinions regarding excess cancer risks.

Note: 0: No NDEA was reported, so no maximum LADD or cancer risk were calculated.

Table 3. Combined excess cancer risks for NDMA + NDEA from valsartan based on data from various companies*

Company*	Combined Risk – Low Average NDMA + NDEA Dose	Combined Risk – Maximum Average NDMA + NDEA Dose
Prinston	5.89×10^{-5}	9.01×10^{-5}
Aurobindo	2.98×10^{-9}	2.05×10^{-6}
Hetero	8.34×10^{-8}	1.08×10^{-7}
Mylan	1.30×10^{-6}	1.23×10^{-5}
Teva	5.95×10^{-9}	1.15×10^{-4}
Torrent	2.06×10^{-6}	7.27×10^{-5}

*Data on NDMA and NDEA levels used in calculations were from FDA's Website – "Laboratory Analysis of Valsartan Products" (FDA, 2019b).

**Duration of exposure: Prinston, 3 years; Aurobindo, 2 years; Mylan, 6 years: Teva, 4 years; and Torrent, 3 years.

In EMA's (2020b) document, *Lessons Learnt from Presence of N-Nitrosamine Impurities in Sartan Medicines*, a similar statement is made, and EMA states that these estimates are "worst-case," based on "very conservative" animal extrapolation, resulting in "very low" risks. They also discussed the importance of not stopping treatment without speaking to a health professional, and the uncertainty surrounding cancer screening or monitoring:

> *The Article 31 review of sartans and the recalls of some medicines generated worldwide interest in the media and among patients and healthcare professionals. Questions raised by the public concerned why regulators allowed N-nitrosamines to be present in sartans in the first place, whether other medicines were affected and what risks patients had been exposed to. On 31 January 2019, EMA's CHMP concluded the review,[20] publishing a final retrospective risk estimate as follows:*
>
>> '…if 100,000 patients took valsartan from Zhejiang Huahai (where the highest levels of impurities were found) every day for 6 years at the highest dose, there could be 22 extra cases of cancer due to NDMA over the lifetimes of those 100,000 patients. NDEA in these medicines could lead to 8 extra cases in 100,000 patients taking the medicine at the highest dose every day for 4 years.[21,22]
>
> *These risk estimates, based on worst-case scenarios for valsartan consumption and a very conservative extrapolation from animal studies, were considered low. Furthermore, for the vast majority of sartan medicines, N-nitrosamines were either not found or were present at very low levels. Given the greater risk to patients from stopping necessary treatments, EU and national authorities advised patients throughout the*

review not to stop taking their sartan medicines without speaking with their healthcare professional.

On the question of protecting patients' health, the CHMP did not find evidence to support cancer screening or additional monitoring of patients exposed to N-nitrosamines. First, the theoretical risk of cancer was very low and was itself based on a worst-case scenario. Second, the screening methods themselves carry risks for patients. Third, there was considerable uncertainty as to which organs or tissues could be at risk from cancer.

A similar discussion on this topic was recently presented by Elder et al. (2021):

During 2019, EMA published an updated risk assessment based on a potential "worst case scenario", where they assessed joint exposure to the highest observable levels of NDEA for 4.6 years, between the years 2011 to 2015, and to NDMA for 6 years, between the years 2012 to 2018. This resulted in a cumulative theoretical excess risk of cancer of 29.5/100,000 or 1/3390, i.e. 0.029% using ICH M7(R1) approaches.[49] *This was then compared to the lifetime risk of cancer in the EU of approximately 50%, and on that basis, this excess risk was considered to be very low. Excess risk refers to the excess rate of cancer associated with exposure to these substances.*

5.1.3.1 Permitted Daily Exposure (PDE) Limits for NDMA and NDEA

Shortcomings of the TD^{50} approach and of the use of AIs has been noted. For example, the Ad-Hoc Expert Group (as part of the EMA's assessment) (EMA, 2020a), discussed their concerns regarding the shortcomings of the TD_{50} approach and communicated their preference for the use of the $BMDL_{10}$ model (EMA, 2020a) (emphasis added):

The ad-hoc expert group expressed preference for the $BMDL_{10}$ model to define usable point of departure metrics, stating however that in certain cases the TD_{50} model could be used. This approach is also harmonised across PROAST and BMDS software for quantal cancer bioassay data. The model averaging approach was also considered more suitable and easier and could overcome considerations with model selection. The BMDL is calculated as lower confidence limit (usually 90%) of a dose corresponding to a defined increase of a toxicological effect compared to controls. This increase is called benchmark response (BMR) or critical effect size (CES e.g. 5 or 10%). The corresponding dose is called Benchmark dose (BMD). <u>Major limitations were identified</u> by the Ad-hoc expert group with the TD_{50} approach. <u>The '1 in 100,000' risk of cancer is the chance of the rodent species developing cancer, not humans</u>. There are <u>no adjustment factors for extrapolation from animal to humans</u> in this calculation. This has been accepted over the years, as the linear extrapolation provides such a low number, but <u>this should be considered when interpreting this value and performing risk evaluations</u>. <u>BMDL methodologies have the advantages that confidence intervals are used, whole dose response is considered, and</u>

> *covariate analysis can be applied. The BMDL analysis is accessible (e.g. online PROAST) and makes no assumptions about linearity or threshold. The use of this method would ensure a harmonised approach with the method used by EFSA.*

Johnson et al. (2021), in their recent publication on permitted daily exposure (PDE) limits, make the following important points about the shortcomings of the derivation and use of the AI values for NDMA and NDEA using the method of FDA/EMA:

> *The estimates represent extremely conservative AI values for human risk assessment, as they do not consider the full character of the dose–response relationship.* (Emphasis added)
>
> And,
>
> *It is now known that carcinogenesis is a multifactorial process involving mutagenic and non-mutagenic pathways and importantly the mutagenic 'adverse outcome pathway' is not linear, with molecular initiating events (adducts) and key events (mutations) being repaired and/or simply not leading to a deleterious effect (Yauk et al., 2015). Furthermore, it is increasingly accepted that threshold mechanisms exist for mutagenic carcinogens (MacGregor et al., 2015a, 2015b) and an extensive analysis of carcinogens has showed that 'at non-toxic doses' thresholds exist for the induction of experimental cancer for all types of carcinogen*, [sic] *including NDMA (Kobets and Williams, 2019).* (Emphasis added)
>
> And,
>
> *Although regulatory authorities generally use the linear extrapolation approach to ensure the safety of a population exposed to a DNA-reactive carcinogen, its application for NDMA and NDEA does not acknowledge the fundamental scientific shift in the quantitative approaches now advocated for regulatory interpretation of mutagenicity dose–response data (Heflich et al., 2020; White et al., 2020). Furthermore, NDEA has been shown to exhibit a potential 'threshold' for carcinogenicity (Waddell et al., 2006). Indeed, the current position on nitrosamines in drug product do not utilize ICH M7 guideline options for instances when DNA repair mechanisms (i.e., those that can lead to compensatory responses at low dose exposures) are well documented (ICH, 2017).*
>
> And,
>
> *Terminology around the background levels of adducts and mutations, must be clearly defined when using mutation data for risk assessment purposes. Endogenous sources of DNA damage are defined here as including reactive oxygen species, formaldehyde, as well as sources such as gut nitrosation and cellular metabolism. Exogenous sources can be divided into two distinct categories, which are from environmental exposures including food*

> *and water, or from drug-related factors including impurities. <u>Endogenous damage is not fully considered with the linear approach</u>.* (Emphasis added)
>
> And,
>
> *We consider that the application of the BMD should inform how N-nitrosamines and other DNA-reactive mutagens are assessed for regulatory purposes. In order for health authorities to support a move from the use of TD50 values for linear extrapolation for risk assessment toward the PDE approach for NDMA, NDEA, and other nitrosamines, there is a need for robust evidence around the underlying mechanisms by which alkylating nitrosamines cause DNA damage and cancer at low concentrations. A "threshold mechanism" with a clear PoD has been clearly presented for many alkylating agents (Muller et al., 2009; Muller & Gocke, 2009). Although chemicals such as NDMA and NDEA have quite diverse adducts spectrums, the most mutagenic and prevalent adducts are those detailed above. <u>These DNA adducts are subject to mechanism-based thresholds linked to DNA repair, especially in the low dose region often exemplified by human exposures to impurities in pharmaceutical preparations</u>.* (Emphasis added)

As an alternative to the AI (as used for NDMA/NDEA by the FDA/EMA), Johnson (2020) and Johnson et al. (2021) point to the derivation of safe levels of NDMA and NDEA using the PDE method based on one of the options provided by ICH M7 (FDA 2018) for use with mutagenic impurities in pharmaceuticals with "evidence for a practical threshold." For instance, ICH M7 (FDA 2018) states:

> *The existence of mechanisms leading to a dose response that is non-linear or has a practical threshold is increasingly recognized, not only for compounds that interact with non-DNA targets but also for DNA-reactive compounds, whose effects may be modulated by, for example, rapid detoxification before coming into contact with DNA, or by effective repair of induced damage. The regulatory approach to such compounds can be based on the identification of a No-Observed Effect Level (NOEL) and use of uncertainty factors (see ICH Q3C(R5), Ref. 7) to calculate a permissible daily exposure (PDE) when data are available.*

In support of this, Johnson et al. (2021) note the body's repair capability that results in a "practical threshold" for mutation at low doses of NDMA and NDEA:

> *The DNA repair enzyme, methylguanine DNA-methyltransferase can restore DNA integrity via the removal of alkyl groups from guanine in an error-free fashion and this can result in nonlinear dose responses and a point of departure or "practical threshold" for mutation at low doses of exposure. Following International recommendations (ICHM7; ICHQ3C and ICHQ3D), we calculated permissible daily exposures (PDE) for NDMA and NDEA using published rodent cancer bioassay and* in vivo

mutagenicity data to determine benchmark dose values and define points of departure and adjusted with appropriate uncertainty factors (UFs).

Thus, using a benchmark dose (lower confidence limit) ($BMDL_{10}$) of 0.062 mg/kg based on the rat liver cancer bioassay data of Peto et al. (1991), a body weight of 50 kg, and a combined uncertainty factor of 500, the PDE_{cancer} for NDMA was determined to be 6,200 ng/person/day by Johnson. The PDE_{cancer} for NDEA of 2,200 ng/person/day was based on the $BMDL_{10}$ of 0.022 mg/kg from Peto et al. (1991) rat liver cancer data, a body weight of 50 kg, and a combined Uncertainty Factor of 500. Johnson (2020) also notes that NDMA has no to low mutagenic activity in tissues other than the liver (citing Suzuki et al., 1996), and it is negative for gene mutation in the bone marrow (citing Jiao et al., 1997). As noted by Johnson et al. (2021) this PDE, derived using a benchmark approach, provides "a more robust assessment of exposure limits compared with similar linear extrapolations and can better inform risk to patients exposed to the contaminated sartans." The advantages of the use of the benchmark dose approach over have been noted—e.g., by the European Food and Safety Authority (EFSA, 2017) and others (e.g., White et al., 2020).

Based on the data on LADDs provided above in Tables 1 and 2, none of the LADDs are above the PDE_{cancer} values for either NDMA (6,200 ng/person/day) or NDEA (2,200 ng/person/day) derived by Johnson et al. (2021).

5.1.3.2 Less-than-Lifetime AIs for NDEA

Another alternative method that has been used as a safe exposure limit for impurities is the less-than-lifetime (LTL) AI. Bercu et al. (2021) recently derived AIs for NDEA in an LTL analysis. These authors note that ICH M7(R1) guidelines discuss a framework to assess the potential carcinogenic risk of LTL exposures to mutagenic and carcinogenic pharmaceutical impurities in instances where the medication is not taken for an individual's lifetime. These LTL values were based on empirical TD_{50} values for NDEA. The goal of the study was to determine whether applying the LTL framework of ICH M7 would control exposure to what would be considered an acceptable excess cancer risk for humans. Bercu et al. (2021) used NDEA as an example compound. The lowest AIs calculated for varying durations of exposure for ≤1 month, >1 month – 10 years, and >10 years to a lifetime were 52,820 ng/day, 2,360 ng/day, and 30 ng/day, respectively. Note that the AI calculated for the lifetime exposure was very close to the 26.5 ng/day value derived by the EPA/EMA for NDEA. Bercu et al. (2021) concluded:

The LTL framework included in ICH M7 for Class 1–3 pharmaceutical impurities is of critical importance to derive appropriate AIs that are specific to the duration of a licensed treatment or for a clinical trial. The LTL AIs were designed to be conservative, with safety factors increasing for shorter exposures. Empirical carcinogenicity data from different NDEA exposure durations indicate that the cancer risk from the ICH M7 derived LTL AIs would be below a 1 in 100,000 [1 x 10^{-5}] *excess cancer risk and below a 1 in 1 million excess cancer risk for extremely short (<6 months) durations. For NDEA, the LTL AIs that follow the ICH M7 framework and would be protective from a patient safety perspective in Table 6. N-Nitrosamines, despite having the potential to be potent mutagenic animal*

carcinogens, should be controlled using the same ICH M7 framework for LTL exposures applied to other classes of compounds which are potential mutagenic carcinogens.

None of the NDEA values detected in valsartan (FDA, 2019b) for any of the companies exceeded the ">1 month to 1 year" exposure duration of 2,360 ng NDEA derived by Bercu et al. (2021).

5.1.3.3 Comparison of NDMA/NDEA Cancer Risks to Background Cancer Risks

The plaintiffs' theoretical excess cancer risk from exposure to NDMA- and/or NDEA-related valsartan can be compared to other cancer risks. As shown above, the range of theoretical cancer risks that could be associated with combined exposure to NDMA and NDEA for all valsartan brands for the low average and maximum average excess cancer risks range from 2.98×10^{-9} to 7.52×10^{-5}. As shown in Table 4 below, the cancer risk just from endogenous NDMA exposure is 111- to 5,033,557-fold higher than combined exposure to NDMA + NDEA (assuming an individual consumed NDMA/NDEA-containing valsartan for the maximum time the manufacturers had the product for sale in the United States).

The plaintiffs' theoretical excess cancer risk from exposure to NDMA- and/or NDEA-related valsartan can be compared to the actual risk from developing cancer that we all face (this will be discussed in more detail later). Over our lifetimes, we all face a real, substantial risk of developing cancer. The overall lifetime risk for men is approximately 1 in 2 or 4.1×10^{-1}, and for women, the risk is approximately 1 in 3 or 3.9×10^{-1}. This indicates that the plaintiffs' *actual* background risk of developing cancer is approximately 5,319- to 134,228,188-fold higher than any theoretical risk from exposure to NDMA or NDEA from valsartan. These calculations show that the risks from NDMA and/or NDEA in valsartan are not meaningfully increased compared to the risks from exposure to endogenously form NDMA or background cancer risks.

Table 4. Theoretical excess risks from valsartan containing NDMA compared to various other cancer risks

Scenario	**Lifetime Excess Cancer Risk (or Range)**
Plaintiffs' Exposure to NDMA + NDEA from Valsartan	2.98×10^{-9} to 7.52×10^{-5}
Lifetime Cancer Risk from Background Endogenous NDMA	8.4×10^{-3} to 1.5×10^{-2}
Background Lifetime Risk of Developing Cancer in the US (Women)	3.9×10^{-1}
Background Lifetime Risk of Developing Cancer in the US (Men)	4.1×10^{-1}

Sources: Chowdhury (2014); Siegel et al. (2021).

5.1.4 Opinion #4 — The plaintiffs' background exposure to NDMA, NDEA and other nitrosamines is orders of magnitude higher than the small concentrations of NDMA/NDEA that might be present in their valsartan.

We are all exposed to NDMA, NDEA, and other nitrosamines on a daily basis. Other potential exposures to NDMA and other nitrosamines include food, drinking water, alcohol, tobacco, air, cosmetics, etc. (FDA, 2021c). These exposures occur over a lifetime and are far higher than the exposure to NDMA and/or NDEA that may have been experienced as a result of the exposures from use of valsartan.

5.1.4.1 N-Nitrosamines

N-Nitrosamines (NOCs) are compounds that are characterized by a nitroso group bonded to an amine. There are approximately 300 congeners that form the group nitrosamines, and this group of compounds has a near ubiquitous presence. It has been reported that over 90% of the 300 NOCs have been shown to be carcinogenic in animal experiments (FDA, 2021d). Humans can be exposed to a wide variety of NOCs from exogenous or endogenous sources (Tannenbaum et al., 1991; Tricker, 1997; Gushgari and Halden, 2018).

Prior to 1956, most of the interest in N-nitroso compounds was related to their industrial applications. After that time, it was discovered that the nitroso compounds occurred naturally in the environment, and also that there was a large potential for endogenous formation of these compounds (Sander et al., 1968, as cited by Tricker, 1997). Even as early as 1978, the National Academy of Sciences stated that *in vivo* or endogenous formation of nitrosamine could be the largest contribution to body burden for the general population (Tricker, 1997).

It has been reported that endogenous synthesis of NOCs could contribute to 45%−75% of total human exposure, and that recent studies in humans have shown that endogenously formed NOCs could be as much as 30-fold higher than that from dietary exposures (Tricker, 1997; Jakszyn and Gonzalez, 2006; Gushgari and Halden, 2018). Gushgari and Halden (2018) note the limited contribution of exogenous source of nitrosamines compared to endogenous sources: "With exogenous exposure only accounting for 3% of the total estimated daily exposure, it is unlikely that avoidance of N-nitrosamine contaminated products would result in a significant reduction of N-nitrosamine exposure from both exogenous and endogenous sources combined."

Exogenous sources of nitrosamines include (Chowdhury, 2014; Gushgari and Halden, 2018):

- Diet [e.g., preformed nitrosamines in cured and smoked meats; pickled and salty preserved foods; foods that have malt added to them (beer, whiskey)]
- Tobacco smoking
- Workplace
- Drinking water
- Indoor and outdoor air

- Cosmetics and personal care products
- Rubber and latex products (e.g., car tires, childcare products, rubber balloons, condoms).

Endogenously formed nitrosamines can originate from:

- Formed from nitrate and nitrite (e.g., sodium nitrite used as preservative)
- Nitrite formed in humans from oral reduction of salivary nitrate (vegetables and drinking water are two main sources of nitrate intake)
- Inhalation of ambient nitrogen oxides
- Cell-mediated nitrosation
- Bacterial nitrosation
- Some chronic inflammatory conditions result in over-production of nitrosating agents (e.g., precancerous conditions of gastric and esophageal cancer).

That endogenous nitrosamines account for a large source of our exposure has been recognized by the National Toxicology Program (2016) and others (e.g., Gushari and Holden, 2018):

> *Although food and tobacco products are important sources of external exposure to N-nitrosamines, exposure also occurs from nitrosamines produced internally in the digestive tract (Hotchkiss 1989). About 5% of ingested nitrates are reduced to nitrites in saliva (NRC 1995). These nitrites can subsequently react in solution with secondary and tertiary amines, as well as N-substituted amides, carbamates, and other related compounds, to form N-nitroso compounds within the gastrointestinal tract (Mirvish 1975, Hotchkiss 1989). This internal formation is a major source of human exposure to N-nitrosamines.* (NTP, 2016)

> *While N-nitrosamine exposure from various matrices can account for upwards of 25,000 ng/day per person it is important to consider this exposure level alongside endogenous N-nitrosamine formation. Significant endogenous N-nitrosamine formation has been identified and is considered to be the result of a combination of endogenous nitrosation mainly in the gastrointestinal tract (Hrudey et al., 2013), cell-mediated nitrosation, bacterial nitrosation, and also a result of inhalation of ambient nitrogen oxides (Tricker, 1997). The reactivity and stability of nitrogen and sulfur containing compounds causes favorable biological conditions for endogenous N-nitrosamine formation but has been shown to be inhibited by the presence of vitamins C and E, as well as the S-nitrosation of thiols (Tricker, 1997). Recent literature suggests that endogenous formation of N-nitrosamines governs human exposure to these compounds and may account for 97% of the total N-nitrosamine load an individual may experience (Jakszyn and Gonzalez, 2006). With exogenous exposure only*

> *accounting for 3% of the total estimated daily exposure, it is unlikely that avoidance of N-nitrosamine contaminated products would result in a significant reduction of N-nitrosamine exposure from both exogenous and endogenous sources combined.* (Gushari and Holden, 2018)

5.1.4.2 Total N-Nitrosamines (TNA)

We are all exposed to NDMA and NDEA, as well as other *N*-nitrosamines, on a daily basis. At least 24 nitrosamine compounds make up the total *N*-nitrosamine (TNA) group of *known* and *suspected carcinogens*. Two of these are known human carcinogens—*N*-nitrosonornicotine (NNN) and 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)—which are tobacco-specific. Depending on one's lifestyle choice, the maximum daily TNA exposure (non-occupational) in the United States has been estimated at 25,000 ± 4,950 ng/day, based on the following exposure categories (Gushgari and Halden, 2018):

- Tobacco products — 22,000 ± 4,350 ng/day[8]
- Food — 1,900 ± 380 ng/day
- Alcohol — 1,000 ± 200 ng/day
- Drinking water — 120 ± 24 ng/day.

The lower bound of exposure for TNAs was estimated to be 1,900 ± 380 ng/d. TNAs can also be found in various personal care products such as lotion, shampoo, soap, and cosmetics (Gushgari and Halden, 2018).

5.1.4.3 NDMA

NDMA is a semi-volatile organic chemical that forms during both industrial and natural processes. It can be found in air, soil, and water. Release into the environment can possibly occur from industries such as tanneries, pesticide manufacturing plants, rubber and tire manufacturers, fish processing, foundries, and dye manufacturers (ATSDR, 1989). NDMA can be formed in drinking water via reaction with disinfectants (e.g., chlorine, chloramines) and alkylamines, nitrosating agents, or ammonia (Chowdhury, 2014). Individuals can be exposed to NDMA from various sources such as those listed in Tables 5 and 6 below.

[8] Note that the CDC (2020a) reports that, among adults in the United States, the number of current smokers ranges from ~9 of 100 adults in Utah (9%) to 25 of every 100 adults in West Virginia (25.2%), with an average of 14 of 100 adults (14%).

Table 5. Sources of exposure to NDMA for the general population

• Consuming food that contains nitrosamines (e.g., smoked or cured meats) • Ingesting food that contains alkylamines (which can cause NDMA to form in the stomach) • Drinking contaminated water • Drinking malt beverages (such as beer and whiskey) that may contain low levels of nitrosamines formed during processing • NDMA-containing toiletry and cosmetic products (e.g., shampoos and cleansers)	• Cigarette smoke (smoking or environmental tobacco smoke [ETS]) • Chewing tobacco • Automobile exhaust • Pesticides • Workplace exposure to NDMA (tanneries, pesticide manufacturing plants, and rubber and tire plants) • Interior air of cars

Sources: ATSDR, 1989; WHO, 2002; NTP, 2016.

Table 6. Foods that contain NDMA

• Cured meat (bacon) • Fish and fish products • Cheese • Beer • Whiskey • Milk and milk products	• Cereals • Baby foods • Beverages • Fruits • Vegetables

Sources: ATSDR, 1989; WHO, 2002; Chowdhury, 2014; EPA, 2014.

The fact the exposure to NDMA is commonplace is even recognized by FDA; they acknowledge that NDMA is known to be found throughout the environment in water and foods such as vegetables, dairy products, and cured and grilled meat (FDA, 2021c). FDA (2018c) provided the following daily estimated doses of NDMA from various foods (Table 7):

Table 7. Estimated range of daily NDMA dose for selected foods

Food Item	Estimated Daily Range of NDMA Intake*
Bacon	70–90 ng
Grilled meat	6–130 ng
Cured meat	4–230 ng
Smoked meat	4–1,020 ng

* Recommended daily food consumption rates based on "Dietary Guidelines for Americans 2015–2020."
Source: FDA (2018c).

Doses of various nitrosamines from food are also provided in the literature. For example, Stuff et al. (2009) calculated the dose of NDMA and NDEA (and other compounds) in various foods in µg per 100 g serving (~3.5 ounces) (Table 8). For some of these foods, just one 100-g serving contains a dose of NDMA or NDEA higher than the FDA's AIs of 96 ng/day NDMA and 26.5 ng/day NDEA in a 320-mg valsartan tablet.

Table 8. NDMA and NDEA doses from food

	µg/100 g								
	NDMA	NPYR	NPIP	NDEA	NDBA	NMOR	NPRO	NTCA	NTHZ
Peas		0.025					0.300		
Whole milk	0.014	0.003	0.003						
Margarine	0.026					0.049			
French fries, fried potatoes	0.024	0.041							
White Wine	0.025	0.109							
Butter	0.026					0.049			
Refried beans or pinto beans	0.033								
Rolls, buns, muffins, bagels	0.050	0.009		0.023					
Cottage cheese	0.076	0.004	0.009	0.057				1.500	
Fried fish	0.169	0.003		0.088	0.004		1.200	4.660	0.018
Beer	0.202								
Hot dogs or franks	0.221							8.950	0.372
Bacon	0.454	2.129	0.049	0.067	1.365		1.000	142.742	2.643
Ham	0.490	0.534	0.004	0.149	0.458	0.286	5.752	46.130	0.154
Sauerkraut	0.660	0.555	0.220	0.079			2.095	0.900	
Oysters	1.139	0.038		0.109		0.007	5.416	0.864	
Sausage or chorizo	10.941	0.086	0.001	0.040		0.052	1.720	11.896	0.172

Source: Stuff et al. (2009).

As stated above, endogenous formation of NDMA occurs in humans. Various estimates have been made based on (1) blood levels: mean of 100,000 to 2,480,000 ng/day (maximum up to 4,350,000 ng/day); (2) mean levels of DNA adducts in leukocytes: 1,360,000 ng/day (maximum of 17,000,000 ng/day); and (3) urinary excretion: <250,000 to 6,400,000 ng/day (Hrudey et al., 2013; FDA, 2021d). Other comparisons can be found in Table 9 below.

Table 9. NDMA doses from commonplace exposures compared to FDA's AI

NDMA Source	NDMA Dose
Amount of NDMA from various food items (milk, cheese, sausage, etc.) (Stuff et al., 2009)	14−10,941 ng/100 g serving
NDMA exposure for smoker (from 1 pack-per-day) (WHO, 2002)	80−5,600 ng/day
WHO acceptable level of NDMA in drinking water (assumes 2 L water/day @ 100 ng/L limit) (WHO, 2008)	200 ng/day
NDMA exposure to indoor environmental tobacco smoke (WHO, 2008)	3,500 ng/day
Range of maximum daily intake of NDMA (age 20–59 years) (0.085–0.126 µg/kg-bw/day x 70 kg-bw) (air+water+food+indoor air ETS + groundwater) (WHO, 2002)	5,950–8,820 ng/day
Estimated mean endogenous NDMA production (humans) (Hrudey et al., 2013)	100,000–2,480,000 ng/day

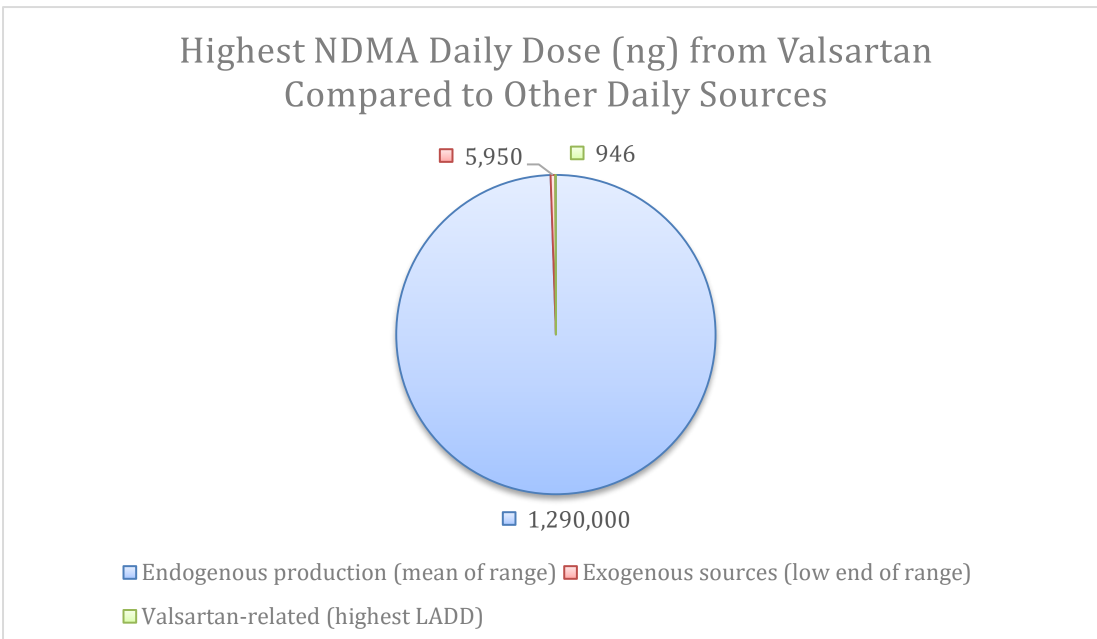

Figure 6. Comparison of lifetime dose of NDMA from valsartan-related NDMA (highest LADD in ng) compared to daily doses from common sources

5.1.4.4 NDEA

NDEA is a nitrosamine that is mostly used as a research chemical currently. Previously, it was used as a lubricant and gasoline additive, antioxidant, plastics stabilizer, copolymer softener, and in the synthesis of 1,1-diethylhydrazine. Individuals can be exposed to NDEA via ingestion, inhalation, and dermal contact. Exposures can occur from the presence of NDEA in food, beverages, tobacco smoke, and drinking water. The intake of NDEA has been estimated to be a few micrograms per day (NTP, 2016). Individuals may be exposed to NDEA from sources such as those listed in below (NTP, 2016):

- Consuming foods that contain NDEA (e.g., cheese, soybeans, soybean oil, fish, cured meats)
- Alcoholic beverages containing NDEA
- Drinking water
- NDMA-containing toiletry and cosmetic products (e.g., shampoos and cleansers)
- Cigarette smoke (smoking or environmental tobacco smoke [ETS])
- Workplace exposure to NDEA.

5.1.5 Opinion #5 — The plaintiffs' alleged exposure and excess theoretical risk to NDMA and/or NDEA is within the background range that is considered acceptable by regulatory agencies.

Typically, the regulatory agencies (including EPA) have selected a risk range of 10^{-4} to 10^{-6} as the acceptable risk range. In numerous policy statements concerning the risks posed by water contaminants or for setting cleanup guidelines at Superfund or RCRA sites, EPA has used the 10^{-4} to 10^{-6} range. For example, Travis et al. (1987) reviewed the risks associated with 132 federal regulatory decisions involving environmental carcinogens to determine the level of risk that led to regulatory action. That analysis revealed that an exposure situation that involved a risk from a potential chemical exposure of 4×10^{-3} triggered a regulation, and regulatory actions were never taken to reduce upper-bound cancer risks below 1×10^{-6}. Regulatory decisions made at levels between 4×10^{-3} and 1×10^{-6} were based on population size, costs, and technical feasibility (Travis et al., 1987; Travis and Hattemer-Frey, 1988, Malander, 1997). In addition, Malander (1997) analyzed the issues of acceptable carcinogenic risk levels in various regulatory programs, and his discussion of the subject was published by the EPA as part of a set of issue papers on risk-based corrective actions. These analyses by Travis and others have been borne out in the range of "acceptable risks" that have been applied by the EPA across its various regulatory programs, as well as the environmental programs of other governmental agencies. For example:

- 10^{-4} to 10^{-6} — the cleanup policy under the EPA Superfund Cleanup Program of the National Oil and Hazardous Substances Pollution Contingency Plan.
    - In 1990 the EPA published its 40 CFR Part 300, final rule of the National Oil and Hazardous Substances Pollution Contingency Plan (38 FR 8665). At page 8848, the Federal Register states: "For known or suspected carcinogens, acceptable exposure levels are generally concentration levels that represent an excess upper bound lifetime cancer risk to an individual of between 10^{-4} and 10^{-6} using information on the relationship between dose and response" (EPA, 1990).
    - EPA's Region 4 published supplemental guidance to RAGs (its various Risk Assessment Guidance documents) in November of 1995 Bulletin No. 5, which was updated in 2018. This guidance document states that, generally, a cumulative site risk above 10^{-4} is used as a remediation trigger.

It states further that the site-specific remedial goal options should contain a table of media-specific cleanup levels for each chemical of concern (COC) and media of concern, and this table should present cleanups levels for 10^{-6}, 10^{-5}, and 10^{-4} risk levels for each carcinogenic COC (EPA, 2018a).

- A letter dated April 22, 1991, from Don R. Clay, Assistant Administrator, sends OSWER (Office of Solid Waste and Emergency Response) directive 9355.0-30 (EPA, 1991a) to the directors of waste management or emergency and remedial response programs in all ten of the EPA's regional offices. The subject of the letter was the "Role of the Baseline Risk Assessment in Superfund Remedy Selection Decisions." The purpose of the letter was to clarify the role played by the baseline risk in developing remedial alternatives and support for risk management decisions made during Superfund actions. It is noted that site risks of less than 10^{-4} and with hazard quotients less than 1.0, that action was generally not warranted unless drinking-water standards were exceeded. It notes that circumstances could alter this decision for risks slightly less than or higher than 10^{-4} based on site-specific conditions. This is stated at page 4 of this letter:

> *Generally, where the baseline risk assessment indicates that cumulative site risk to an individual using reasonable maximum exposure assumptions for either current or future land use exceeds the 10^{-4} lifetime excess cancer risk end of the risk range, a site is determined to pose an unacceptable risk to human health and action under CERCLA Section 104 or 106 is justified. In other words, for sites where the cumulative site risk to an individual based on reasonable maximum exposure for either current and future land use is less than 10^{-4}, action generally is not warranted. ... Although the Agency has expressed a clear preference for cleanups achieving the more protective end of the range (i.e., 10^{-6}), waste management strategies achieving reductions in site risks anywhere within the risk range may be deemed acceptable. Furthermore, the upper boundary of the risk range is not a discrete line at 1×10^{-4} , although EPA routinely interprets 10^{-4} to mean 1×10^{-4} in making risk management decisions. Rather, the decision whether a specific risk estimate for a site/pathway around 10^{-4} (e.g., 4×10^{-4}) is considered acceptable is based on site-specific conditions, including any remaining uncertainties on the nature and extent of contamination and associated risks. Therefore, EPA may consider risk estimates slightly above the 1×10^{-4} level to be protective. Conversely, in limited situations EPA may determine that risks below 1×10^{-4} are not sufficiently protective and, therefore, warrant remedial action.*

- 10^{-4} to 10^{-6} — EPA drinking-water standards (maximum contaminant levels, or MCLs) under the Safe Drinking Water Act (SDWA) (EPA, 1984, 1991b).

- The 49 Federal Register 24348 (July 12, 1984) states: "Federal regulation for environmental contaminants have generally fallen in the 10^{-4} to 10^{-6} lifetime risk range, as calculated from a linear multi-stage model" (EPA, 1984).
- January 30, 1991, the EPA discusses 40 CFR Parts 141, 142, and 143, and reports proposed national drinking-water standards for various chemicals (56 FR 3526). At pages 3534–3535, this Federal Register document states (emphasis added): "Some commenters point out that the EPA has determined that standards reflecting a 10^{-4} to 10^{-6} risk level are safe and protective of public health even for known or probable carcinogens under other of its authorities… In addition, when EPA establishes MCLs, it considers the cancer risk at the MCL to determine whether they would be acceptable from a safety standpoint. <u>A target risk range of 10^{-4} to 10^{-6} is considered by EPA to be safe and protective of public health.</u>"
- And, on page 3547, section "B.1 Methodology for Determination of MCLs" states (emphasis added): "For category I contaminants, the Agency also evaluates the health risks that are associated with various levels of the contaminants. <u>With the goal of ensuring the maximum risk at the MCL falls within the 10^{-4} to 10^{-6} risk range that the Agency considers protective of public health, therefore achieving the overall purpose of the SDWA.</u>"
- Also, in the EPA's Drinking Water Standards and Health Advisories Tables' document (EPA, 2018b), it is stated that the Health Advisory Program sponsored by the EPA Office of Water publishes concentrations of drinking-water contaminants for cancer at the 10^{-4} cancer risk, adding that the Office of Water also advises consideration of more conservative cancer risk levels of 10^{-5} and 10^{-6} if those are considered more appropriate for exposure-specific risk assessment.

- EPA (2000), in one of their risk communications documents, discusses the concept and conservative nature of acceptable risk:

> *EPA generally considers an upper-bound lifetime cancer risk to an individual of between 10^{-4} and 10^{-6} as a safe range. A risk of 10^{-4} represents a probability that there may be one extra cancer case in a population of 10,000. A 10^{-6} risk is the probability that there may be one extra cancer case in a population of one million people over a lifetime of exposure to a chemical at the RME dose. This also means that at most, there is one chance in a million of getting cancer from exposure to a specific level of a chemical, under the conditions defined in the risk assessment, over a lifetime (see page 8-27 in RAGS-A).*
>
> *An upper-bound cancer risk estimate ensures that the actual chance of getting cancer will most likely be below EPA's risk estimate. To get an upper-bound risk estimate, EPA chooses the most conservative mathematical model to analyze the data. Also, in the exposure assessment, EPA chooses reasonable maximum exposure. As a result, the cancer risk range that EPA views as acceptable for*

> *soil, air, and water is likely to overstate the actual human cancer risks.*

- OSWER staff have developed a list of various risk definitions to use when interfacing with communities (undated). The following definition was provided for "acceptable exposure level" (or "acceptable risk"):

> *This is a legal term defined in the National Contingency Plan (NCP), which is the that promulgates CERCLA (see below for definition). An acceptable exposure level is the "concentration level of a contaminant to which the human population, including sensitive subgroups, may be exposed without adverse effect during a lifetime or part of a lifetime..." For known or suspected carcinogens, acceptable exposure levels are generally concentration levels that represent lifetime cancer risk to an individual of between 10^{-4} (1 in 10,000) and 10^{-6} (1 in 1,000,000) using information on the relationship between the dose and response.*

5.1.6 Opinion #6 — The extrapolation of animal test results to predict the actual human response is a regulatory assumption associated with great uncertainty.

The shortcomings of animal testing as a predictor of human health effects are numerous and substantial. I will only summarize them in the body of this report; further explanation is contained in Appendix A (which itself is not an exhaustive treatment of the issues).

Although using surrogate animal species to test the potential toxicities that a chemical might induce in humans is a reasonable regulatory approach, the extrapolation of animal findings to predict the human response is fraught with difficulty. It is well known in toxicology that findings in any animal test may vary if one chooses any one of the five key components of all toxicity tests. For example:

a. The specific species selected to be tested

b. The response (effect) selected to be measured

c. The exposure interval over which the chemical is administered to the test species

d. The observation period over which the selected responses is measured

e. The range of doses to be tested.

Perhaps more important is the fact that, while the rodent species used in toxicity tests are generally biologically similar to humans (i.e., humans are another animal species), there can be critical differences in anatomy and biology/physiology between human and rodent species, and even between two different rodent species, and these differences can alter the outcome of the chemical exposure. Even for a relatively simple chemical such as chloroform, rats and mice respond with different toxic effects when exposed to the same concentration. Which effect, then, would one be able to reliably predict is the human response at the same concentrations using only the animal data? Studies have shown that the B6C3F1 mouse and Fischer 344 rat have high background incidence rates of different

types of tumors. For this mouse strain, the liver has a high background tumor incidence, and this is the most common carcinogenic response observed in chemical cancer bioassays using this test strain. But there are many reasons why this promotion of a high background rate would be species- and dose-specific. Thus, the observation of this carcinogenic response in a chemical cancer bioassay test is one of questionable reliability. In fact, using the cancer risk (potency) for a chemical that is derived from species/target organ with a higher background incidence of cancer than that occurring in humans only inflates the risk estimate by a significant but unquantifiable amount. This exaggeration in the cancer potency used for NDEA and NDMA means that any risk assessment using this cancer potency factor should acknowledge the fact the true human risk is actually lower than calculated, and in fact, may be as low as zero.

Likewise, the Fischer 344 rat has a high background incidence of several tumors, one being Leydig cell tumors. But the fact that a chemical produces only this type of tumorigenic response in the Fischer 344 rat is considered to be a test result of no human relevance.

Some chemicals induce Zymbal gland tumors or forestomach tumors in rodent cancer bioassays. But humans do not have these anatomical structures, and therefore, this risk cannot be extrapolated to humans. Likewise, a number of industrial chemicals have induced other types of tumors in animals via species-specific mechanisms that carry no risk of cancer to humans (see Appendix A). Moreover, empirical evidence used to perform comparative analyses of species extrapolations to the actual human toxicity of drugs has shown the very poor predictability of responses seen in rodents. Additionally, rodent test results provide poor predictions of the human response, and in animal cancer bioassays, the positive results seen in one rodent species reliably predict the outcome in the other rodent species less than 50% of the time. If one rodent species only poorly predicts outcomes in another rodent species, there is no reason to believe that rodent tests accurately or reliably predict whether or what levels chemicals will cause adverse effects in humans.

Besides well-recognized, species-specific responses that confound extrapolations of animal results to humans, cancer bioassays have long been criticized for the use of the maximum tolerated dose (MTD). Use of the MTD is an effort to maximize the sensitivity of the animal cancer bioassay, but its use is known to generate a high number of potentially false positive results (i.e., positive results seen only at high doses). In fact, it has been shown that almost half (some 43%) of the positive animal bioassay results would not be observed if the dose were restricted to just half of the MTD. Thus, the animal studies clearly demonstrate that risk will frequently reduce to zero at doses well above those experienced by humans. This finding is not surprising, given that the science of toxicology posits that all toxicities have a threshold and a range of safe doses, and that this is true even for carcinogens.

Ames and Gold (2000) provide an explanation of why low-level chemical exposure in humans likely poses little to no excess cancer risk:

> *About 50% of chemicals - whether natural or synthetic - that have been tested in standard, high-dose, animal cancer tests are rodent carcinogens [1-3]. What are the explanations for this high percentage? In standard*

> *cancer tests, rodents are given a chronic, near-toxic dose: the maximum tolerated dose (MTD). Evidence is accumulating that cell division caused by the high dose itself, rather than the chemical per se, can contribute to cancer in these tests [2,4-14]. High doses can cause chronic wounding of tissues, cell death and consequent chronic cell division of neighboring cells, which is a risk factor for cancer. Each time a cell divides, there is some probability that a mutation will occur, and thus increased cell division increases the risk of cancer. At the low levels of synthetic chemicals to which humans are usually exposed, such increased cell division does not occur. The process of mutagenesis and carcinogenesis is complicated because many factors are involved: e.g., DNA lesions, DNA repair, cell division, clonal instability, apoptosis, and p53 [15,16]. The normal endogenous level of oxidative DNA lesions in somatic cells is appreciable [17]. In addition, tissues injured by high doses of chemicals have an inflammatory immune response involving activation of white cells in response to cell death [18-25]. Activated white cells release mutagenic oxidants (including peroxynitrite, hypochlorite, and hydrogen peroxide). Therefore, the very low levels of chemicals to which humans are exposed through water pollution or synthetic pesticide residues may pose no or minimal cancer risks.*

For all these reasons (and many others), there is considerable uncertainty when extrapolating animal results to predict the human response at any dose. This is why regulatory risk assessments are forced to adopt large safety factors when extrapolating the safe dose from animal studies, to protect against the uncertainty inherently associated with animal-to-human extrapolations. It is also why the EPA has recognized that their IRIS values cannot be used to predict the actual human response to any dose of a given chemical (EPA).[9]

In its sartan cancer risk assessment, EMA (2020a) addressed the extrapolation of the animal-based risk to human risk:

> *The '1 in 100,000' risk of cancer is the chance of the rodent species developing cancer, not humans. There are no adjustment factors for extrapolation from animal to humans in this calculation. This has been accepted over the years, as the linear extrapolation provides such a low number, but this should be considered when interpreting this value and performing risk evaluations.*

EMA (2020a) also recognized the difficulty in extrapolating the results of animal studies from nitrosamine studies to what might be expected in humans because the exposure levels in humans are "far below those than [*sic*] can be experimentally tested and verified in animal studies..."

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[9] Note that the EMA (2020a) states the EPA IRIS cancer slope factors for NDMA and NDEA are similar to the potency ranking calculated by using the harmonic mean TD_{50} of the CPDB.

5.1.7 Opinion #7 — Scientific evidence exists to show that NDMA and NDEA have thresholds.

Papers showing thresholds and/or non-linear dose-response curves for genotoxic endpoints and/or mutagenic/genotoxic carcinogens have been published for several chemicals (e.g., Sofuni et al., 2000; Fukushima et al., 2005, 2012; Kobets and Williams, 2019).

Uncertainties and limitations remain, associated with the models and assumptions used to derive cancer slope factors and to extrapolate low-dose cancer risks using the EPA risk assessment approach (be it via the linearized multistage model or linear extrapolation from a benchmark dose derivation). These problems arise because the EPA continues to default to the assumption that cancer risk must be extrapolated linearly, even though it is now well recognized within the general scientific community that many, if not all, chemical carcinogens have real or practical thresholds, even those chemicals believed to have a mutagenic mode of action (MOA). That this is the current consensus scientific opinion on this subject is perhaps best exemplified by statements found in the most widely recognized and used basic textbook on toxicology—*Casarett and Doull's Toxicology: The Basic Science of Poisons*. In the fourth edition of this textbook, which was published three decades ago, the authors of the chapter on *Carcinogenesis* state:

> *Nevertheless, several lines of evidence suggest that in the human context there are thresholds for DNA-reactive carcinogens.* ... (page 154)
>
> *In summary, carcinogens, both DNA-reactive and epigenetic, act in a dose-dependent fashion, although the dose-response relationships appear to be different. <u>There are observed thresholds for both types of carcinogens in experimental animals and humans</u>.* (Williams and Weisburger, 1991; page 155; emphasis added)

And in the subsequent fifth edition of this textbook published 25 years ago (Pitot and Dragan, 1996; emphasis added):

> *The use of extreme concentrations of a test compound, while useful under some conditions for the identification of a potential carcinogenic risk, may not be required or even useful for human risk estimation. In fact, the use of an MTD can result in a number of confounding results that create difficulty for extrapolation across species including extrapolation from high-dose to low-dose exposure scenarios. Specifically, overt toxicity may result from the administration of high doses of compounds that result in pathologies that are not hinted at with lower-dose administration. In addition, metabolic and repair pathways may be overwhelmed at higher compared with lower doses. <u>These types of factors can lead to a loss in the continuity of the spectrum of toxicities likely to be observed at the lower doses of human exposures, thus hampering extrapolation from observations at the higher dose to possible risks at the human exposure level.</u>*
>
> *Some agents may be mutagenic* in vitro *but fail to demonstrate carcinogenic action in vivo because of a short chemical half-life, rapid excretion of the*

> *test chemical* in vivo*, metabolic detoxification of the ultimate carcinogen, or enhanced detoxification relative to activation* in vivo.
>
> *Models of cancer risk assessment assume that all carcinogens are the same and that there is no threshold for their carcinogenic action. However, it is known that for most carcinogens repair processes are available within the cell. In addition, most early changes are adaptive in nature, and functionally redundant pathways exist to compensate for those changes. While thresholds exist for each of the processes involved in the carcinogenesis process, the default assumption in the risk assessment process is that there is not a measurable threshold.*

Additionally, it should be noted that toxicologists at the 1998 Society of Toxicology meeting voted overwhelmingly to affirm their belief that all carcinogens have thresholds (SOT, 1998). Supporting this decision are the ever-increasing number of papers showing thresholds and/or nonlinear dose-response curves for both genotoxic endpoints and mutagenic/genotoxic carcinogens (e.g., Calabrese and Baldwin, 1998; Kitano et al., 1998; Sofuni et al., 2000; Swenberg et al., 2000; Williams et al., 2000; Sukata et al., 2002; Fukushima et al., 2002, 2003, 2004; Kinoshita et al., 2003; Tsuda et al., 2003; Hoshi et al., 2004; Williams et al., 2004; Doak et al., 2007; Johnson et al., 2009; Gocke and Muller, 2009; Fukushima, 2010). These studies emphasize the fact that certain phases/steps of the carcinogenic process are governed by endpoints that do have thresholds. So, with lower doses, the threshold(s) for one (or more) of these steps is reached, creating a real or practical threshold for the entire carcinogenic process.

Thresholds have been suggested for NDMA and/or NDEA (Waddell, 2003, 2006; Fukushima et al., 2005, 2009, 2012; Fukushima, 2010; Kobets and Williams, 2019).

5.1.8 Opinion #8 — The human body contains multiple repair mechanisms that help overcome one's exposure to chemicals.

5.1.8.1 The Endogenous Exposome

We are all exposed to a multitude of chemicals during our lifetime (as discussed later). The term "exposome" encompasses the "diseases and one's lifetime exposure to chemicals, whether the exposure comes from environmental, dietary, or occupational exposures, or endogenous chemicals..." Specifically, the group of *endogenous* chemicals (in the body) formed from "...normal metabolism, inflammation, oxidative stress, lipid peroxidation, infections, and other natural metabolic processes such as alteration of the gut microbiome..." are those that make up what is known as the "endogenous exposome" (Nakamura et al., 2014). It is estimated that 40,000+ DNA lesions are formed per cell per day in the body as a result of endogenous exposures (e.g., ethylene oxide, formaldehyde, isoprene). Types of DNA lesions include AP sites, 7-(2-oxyoethyl)-G, 8-OxodG, 7-Methylguanine, N2,3-Ethenoguanine, and O6-Methyl dG (Nakamura et al., 2014). In concert with DNA lesions formed from exogenous sources, mutations from endogenous sources (as well as DNA repair) also exist.

5.1.8.2 DNA Lesions and Repair

It has long been accepted than nongenotoxic or epigenetic carcinogens induce cancer via a threshold-dependent process, and so, yield a nonlinear, threshold-dependent dose-response curve. However, it has also become increasingly clear than even carcinogens with mutagenic or genotoxic activity can and do induce tumors via threshold-dependent processes, and so, have nonlinear dose-response curves as well. Not all mutations become fixed and heritable, and not all fixed mutations are in genes relevant to cell growth and differentiation. Further, the multiple mutations required to cause a malignant tumor may involve different genetic mechanisms that a single chemical is not able to cause. Furthermore, unless there is proliferation of the target tissue (i.e., promotion), the mutagenic events alone may not be sufficient to lead carcinogenicity. These considerations explain why biomarkers that reflect chemical/DNA interactions, such as DNA adducts, do not always correlate with carcinogenicity, and why mutagenic chemicals are either not always carcinogenic or do not induce cancer via a mutagenic/genotoxic mechanism (Butterworth, 1990; Barrett, 1993). Some key mechanistic considerations are:

(1) The importance of cellular proliferation in carcinogenicity (i.e., the fact that many mutagenic chemicals induce some basis for cellular proliferation in addition to a key genetic change before a tumor is formed).

(2) The presence of DNA adducts does not necessarily lead to carcinogenicity. Thresholds real and practical have been reported, even for those genotoxic changes thought to be the key event in tumor induction. For example, Poirier and Beland (1992) reported that in four of the nine rodent models they tested, even though DNA adducts were measurable, no tumors formed.

(3) Not all carcinogens are mutagenic, and not all mutagens are carcinogenic. For example:

- The key role played by cell proliferation during hepatocarcinogenesis of 2,4-diaminotoluene has been demonstrated by Cunningham et al. (1991). 2,4-Diaminotoluene and 2,6-diaminotoluene are equally mutagenic in the Ames/Salmonella assay and are both readily absorbed, metabolized, and excreted (Cunningham et al., 1989). In addition, metabolites of both compounds are mutagenic (with metabolic activation). However, Cunningham et al. discovered that these two mutagenic compounds were vastly different in rodent cancer bioassays. 2,4-Diaminotoluene proved to be a potent liver carcinogen, whereas 2,6-diaminotoluene was noncarcinogenic in rodent bioassays. It was determined that the carcinogen 2,4-diaminotoluene caused a dose-dependent increase in cell proliferation of about 10%, and 20% in livers of animals exposed to 12.5 and 25 mg/kg/day, where the noncarcinogen 2,6-diaminotoluene produced no such proliferation (even at doses up to 50 mg/kg/day). Thus, just because a chemical is both mutagenic and carcinogenic does not mean the key step to its carcinogenicity involves

the chemical's mutagenic effects (for another example, see Cunningham et al. (1994).

- Yoshikawa (1996) evaluated whether nongenotoxic hepatocarcinogens caused an increase in cell proliferation after a single administration of each chemical to male F344 rats or male B6C3F1 mice. Almost all hepatocarcinogens tested increased cell division (regardless of whether or not they were genotoxic), indicating that the potential to cause proliferation is common regardless of genotoxicity potential.

- Gold et al. (1989) evaluated the prediction for carcinogenic response between species with regard to mutagenicity. Gold et al. examined evaluations of mutagenicity in Salmonella from compilations for 294 chemicals. While it was reported that a greater proportion of mutagens are carcinogenic than are nonmutagenic chemicals (72% vs. 51%), however, about half of chemicals shown to be animal carcinogens were not mutagenic (79/178, or 44%, as shown in Table 3 on page 214 of this paper).

(4) *In vitro* (test tube) mutagenic assays cannot be used to predict mutagenicity *in vivo* (in the animal).

- *In vitro* tests typically use organisms whose DNA repair capacity is limited or has been removed. Thus, dose-response may be linear when DNA repair enzymes are absent, but threshold dependent and nonlinear when DNA enzymes are present (e.g., Sofuni et al., 2000).

- It has been estimated that more than 100 genes are dedicated to the different types of DNA repair. Types of repair include: (1) direct reversal of DNA damage, (2) base excision repair, (3) nucleotide excision repair, (4) recombination-postreplication repair, and (5) mismatch repair. These repair mechanisms help protect the cell against increases in DNA lesions from both endogenous and exogenous mutagens (Hoffmann, 1984). Ames and associates (1993) estimated that the individual reactive "hits" to DNA per cell per day are on the order of 10^5 (or 100,000) in rats and 10^4 (or 10,000) in humans, as a result of endogenous oxidative reactions alone. But humans have a greater DNA repair capacity, and so are at lower risk from both endogenous and exogenous DNA damage.

- Allavena et al. (1992) demonstrated that not all chemicals that are genotoxic *in vitro* necessarily cause mutations in test animals. The chemicals 2-chloroethanol, 8-hydroxyquinoline, 2,6-toluenediamine, and eugenol are compounds that have been demonstrated to be genotoxins via results from *in vitro* test systems. However, these chemicals did not cause cancer in rodents. When evaluated for their ability to cause mutagenic effects *in vivo* (in rats), aside from an increase in DNA damage and repair in one group of rats dosed with 2,6-

toluenediamine, none of the compounds caused effects indicative of genetic toxicity in the whole animal.

(5) The doses necessary to induce mutation events in the whole animal may be higher than those sufficient to induce tumors in that animal (e.g., see Moore and Harrington-Brock, 2000, regarding TCE). This, in turn, means that at the dose sufficient to induce tumors, other, threshold-dependent biological processes are the key events leading to tumorigenicity. For example, Shaw and Jones have stated:

> *Most genotoxic carcinogens are mutagens, but all mutagens are not necessarily carcinogens, the dose administered being crucial to tumorigenesis… genotoxic carcinogens appear to have a threshold dose below which cancers do not develop… Below the threshold, DNA repair mechanisms correct damage caused by the mutagen and metabolic processes detoxify mutagens and facilitate their transport and excretion from the body. Above the threshold dose, these defense systems are overwhelmed, the cell succumbs to the mutagenic effects of the chemical and the process of carcinogenesis is initiated. It is for these reasons that Ames-positive chemicals do not necessarily cause cancer.* (Shaw and Jones, 1994; page 89)

In short, there are a number of reasons why a carcinogen may be inducing cancer via a nonlinear, threshold-dependent mechanism, regardless of its mutagenicity/genotoxicity status. This, in turn, means that the regulatory default assumption of modeling a chemical's theoretical cancer risk via a linear model can exaggerate the low-dose risk, even for those carcinogens believed to have some mutagenic potential.

The importance of DNA repair and thresholds for mutagens has been discussed in the recent literature (Nakamura et al., 2014; Kobets and Williams, 2019; Hartwig et al., 2020).

In addition, it has been noted that antioxidants such as vitamins C (ascorbic acid) and E can inhibit nitrosamine formation (e.g., Tannenbaum et al., 1991). Tannenbaum et al. (1991) states that nitrosatable amines are found in many foods, while some are formed in the body. When ascorbic acid is administered along with a test compound (e.g., nitrate + L-proline to form N-nitrosoproline), the concentration of the nitrosamine decreases compared to administration without the antioxidant compounds (ascorbic acid). Thus, the presence of these types of compounds in the diet or taken as supplements can potentially decrease the amount of nitrosamine to which an individual might be exposed.

5.1.9 Opinion #9 — The plaintiffs' alleged excess theoretical risk associated with exposure to NDMA and/or NDEA from use of valsartan is lower than the background cancer risks we all face.

5.1.9.1 Introduction

It has been estimated that more than 50% of chemicals tested in rodent cancer bioassays, regardless of whether they are natural or synthetic, have been found to be carcinogenic

based on results of high-dose chronic bioassay results (Ames and Gold, 2000). Gaylor (2005) has estimated that 93% of all chemicals tested would be considered carcinogenic substances if larger animal groups were tested to increase the test's ability to show that smaller changes were statistically significant.

The purpose of this section is to demonstrate that we are all exposed to a multitude of chemicals, including many mutagens and carcinogens in air, water, food, medications, and the workplace. The excess risks from those commonplace background exposures are in the 10^{-3} to 10^{-2} range (i.e., 1 in 1,000 to 1 in 100) when using procedures such as those adopted by the EPA and other regulatory agencies. The sections below describe examples of everyday exposures to mutagens and carcinogenic compounds, and background excess cancer risks from these exposures.

5.1.9.2 Background Baseline Cancer Risks that We All Face

The baseline background *actual*, not *theoretical*, risk that Americans have of developing cancer during their lifetime is high. According to the most recent cancer statistics from the American Cancer Society, the lifetime probability of developing an invasive cancer (all sites, excluding basal cell and squamous cell skin cancers and *in situ* cancers except urinary bladder) is almost *1 in 2* in males (40.5%) and over *1 in 3* in females (38.9%) (Siegel et al., 2021) (see Table 10, reproduced from Siegel et al., 2021).

Table 10. Probability (%) of developing cancer by age intervals and sex in the United States, 2015 to 2017

		Birth to 49	50 to 59	60 to 69	70 and older	Birth to death
All sites†	Male	3.5 (1 in 29)	6.2 (1 in 16)	13.6 (1 in 7)	33.2 (1 in 3)	40.5 (1 in 2)
	Female	5.8 (1 in 17)	6.4 (1 in 16)	10.3 (1 in 10)	26.8 (1 in 4)	38.9 (1 in 3)
Breast	Female	2.1 (1 in 49)	2.4 (1 in 42)	3.5 (1 in 28)	7.0 (1 in 14)	12.9 (1 in 8)
Colon & rectum	Male	0.4 (1 in 254)	0.7 (1 in 143)	1.1 (1 in 92)	3.2 (1 in 32)	4.3 (1 in 23)
	Female	0.4 (1 in 266)	0.5 (1 in 191)	0.8 (1 in 128)	2.9 (1 in 34)	4.0 (1 in 25)
Kidney & renal pelvis	Male	0.2 (1 in 410)	0.4 (1 in 263)	0.7 (1 in 151)	1.4 (1 in 73)	2.2 (1 in 46)
	Female	0.2 (1 in 647)	0.2 (1 in 541)	0.3 (1 in 310)	0.8 (1 in 133)	1.3 (1 in 80)
Leukemia	Male	0.3 (1 in 391)	0.2 (1 in 549)	0.4 (1 in 255)	1.4 (1 in 69)	1.8 (1 in 55)
	Female	0.2 (1 in 500)	0.1 (1 in 834)	0.2 (1 in 427)	0.9 (1 in 110)	1.3 (1 in 78)
Lung & bronchus	Male	0.1 (1 in 776)	0.6 (1 in 163)	1.7 (1 in 58)	5.9 (1 in 17)	6.6 (1 in 15)
	Female	0.1 (1 in 679)	0.6 (1 in 172)	1.4 (1 in 70)	4.9 (1 in 21)	6.0 (1 in 17)
Melanoma of the skin‡	Male	0.4 (1 in 230)	0.5 (1 in 198)	0.9 (1 in 109)	2.7 (1 in 37)	3.7 (1 in 27)
	Female	0.6 (1 in 156)	0.4 (1 in 241)	0.5 (1 in 187)	1.2 (1 in 86)	2.5 (1 in 40)
Non-Hodgkin lymphoma	Male	0.3 (1 in 375)	0.3 (1 in 345)	0.6 (1 in 177)	1.9 (1 in 54)	2.4 (1 in 42)
	Female	0.2 (1 in 523)	0.2 (1 in 463)	0.4 (1 in 242)	1.4 (1 in 73)	1.9 (1 in 52)
Prostate	Male	0.2 (1 in 451)	1.8 (1 in 55)	5.0 (1 in 20)	8.7 (1 in 12)	12.1 (1 in 8)
Thyroid	Male	0.2 (1 in 447)	0.1 (1 in 703)	0.2 (1 in 571)	0.2 (1 in 412)	0.7 (1 in 146)
	Female	0.9 (1 in 114)	0.4 (1 in 258)	0.4 (1 in 283)	0.4 (1 in 263)	1.9 (1 in 53)
Uterine cervix	Female	0.3 (1 in 362)	0.1 (1 in 837)	0.1 (1 in 916)	0.2 (1 in 590)	0.6 (1 in 158)
Uterine corpus	Female	0.3 (1 in 322)	0.6 (1 in 157)	1.1 (1 in 94)	1.5 (1 in 67)	3.1 (1 in 32)

It should be noted that individuals taking valsartan for hypertension—one of the main indications for its administration—typically would be among the older age range of the population. For the time period 2015–2016, the prevalence of hypertension among men and women ages 40–59 years was 37.2% and 29.4%, respectively (see Figure 7 below). For men and women ages 60 years and over, the prevalence was 58.5% and 66.8%. Thus, many of the individuals who are likely to have taken valsartan in this manner will be among those with the highest background risk of developing cancer. For instance, the risk of developing cancer for a 70-year-old male who took valsartan is already 3.3 in 10, or 3.3 x 10^{-1}. Therefore, the magnitude of their background cancer risk compared to their theoretical excess cancer risk from valsartan-related NDMA would be higher.

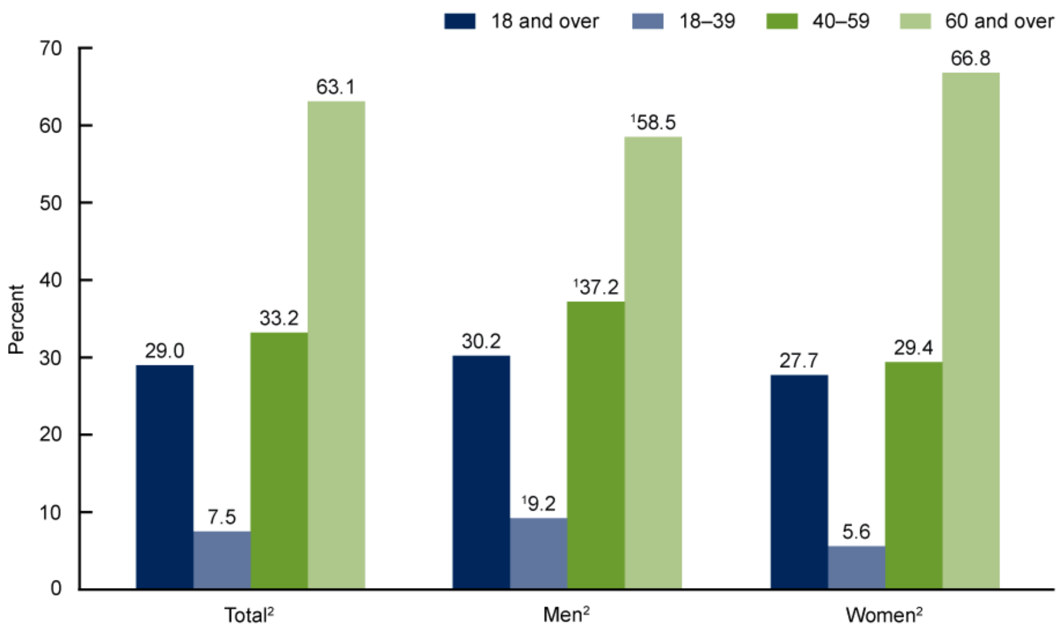
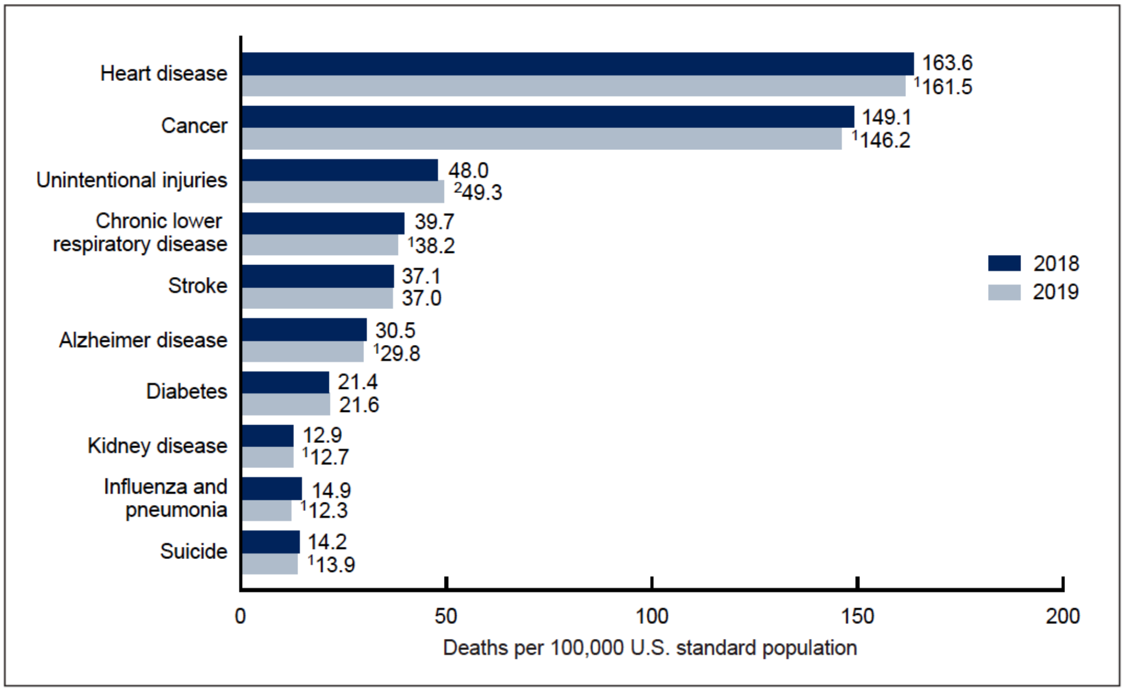


Figure 7. Prevalence of hypertension among adults ages 18 and over, by sex, United States, 2015-2015. Source: Fryar et al., 2017.

5.1.9.3 Background Risk from Hypertension-Related Mortality

One of the indications of valsartan is for the treatment of hypertension—a condition that can result in heart disease, heart attack, stroke, and other diseases that can cause premature death. Approximately nine out of 10 Americans will develop hypertension at some point during their lifetime (CDC, 2020b). Heart disease and stroke are two of the top 10 leading causes of death in the United States (Kochanek et al., 2020; CDC, 2020c) (see Figure 8 below). The importance of seeking the advice of individuals' health-care providers in the use of valsartan can be seen based on these data.



[1]Statistically significant decrease in age-adjusted death rate from 2018 to 2019 ($p < 0.05$).
[2]Statistically significant increase in age-adjusted death rate from 2018 to 2019 ($p < 0.05$).
NOTES: A total of 2,854,838 resident deaths were registered in the United States in 2019. The 10 leading causes of death accounted for 73.4% of all deaths in the United States in 2019. Causes of death are ranked according to number of deaths. Rankings for 2018 data are not shown. Data table for Figure 4 includes the number of deaths for leading causes. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db395-tables-508.pdf#4.
SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality.

Figure 8. Age-adjusted death rates for the 10 leading causes of death in the United States, 2018 and 2019. Source: Kochaneck et al. (2020).

5.1.9.4 Obesity and Other Modifiable Risk Factors that Contribute to Cancer

Important risk factors should be considered as contributors to cancer in the plaintiffs in this case, aside from any low reported valsartan-related NDMA or NDEA exposures. The American Cancer Society stated that approximately 42% of cancer cases and 45% of cancer deaths are linked to modifiable risk factors and are preventable, based on a study from Islami et al. (2018). The main modifiable (i.e., those that can potentially be prevented by an individual) cancer risk factors among the American population are:

- **Cigarette smoking** — accounted for 19% of all cancer cases and almost 29% of cancer deaths
- **Excess body weight** — responsible for 7.8% of cancer cases and 6.5% of deaths
- **Drinking** — linked to 5.6% of cancer cases and 4% of deaths
- **UV radiation** — attributable to almost 5% of cases, but a lower 1.5% of deaths
- **Physical inactivity** — accounted for 2.9% of cases and 2.2% of deaths.

5.1.9.5 Background Exposures and Cancer Risks from the Diet

All individuals are exposed to a wide variety of mutagenic and carcinogenic compounds through diet, exposures that represent a significant increase in background cancer risk. It has been estimated that approximately 35% of all cancer deaths are caused by diet (Doll and Peto, 1981). Doll and Peto (1981) estimated that only about 1% of cancers were due to medical agents or medical practices, with one-half of that risk being due to radiation.

Ames and colleagues have determined that the contribution to human cancer risk was likely to be greater from natural carcinogens found in foods than the man-made chemicals associated with pesticide uses. One principal reason for this is, of course, the fact that vastly larger amounts of carcinogenic chemicals are produced by plants to defend themselves against being eaten, compared to the much smaller amounts of pesticide sprayed on the surface of plants by humans to help repel insects. Ames et al. (1990) and Ames and Gold (2000) estimated that Americans consume about 5,000 to 10,000 different natural pesticides and their breakdown products each day, consuming roughly 1,500 milligrams per day of natural pesticides via their foods. This amount is about 10,000 times greater than the amount of synthetic pesticide residues consumed with these same foods (keeping in mind that the concentrations of natural pesticides in plants are typically measured in the parts per thousand or million compared to parts per billion, the usual level that synthetic residues or water pollution are measured in). In support of this conclusion, Ames et al. (1990) identified 49 natural pesticidal substances and metabolites in cabbage alone (see Table 11). As shown in the table that follows the list of natural pesticides/metabolites, several of these substances have been tested and found to have mutagenic and/or carcinogenic potential based on rodent carcinogenicity tests (as presented in Table 12 below from Ames et al., 1990). The intake of these natural pesticides in the diet varies and would be higher in vegetarians. Ames et al. (1990) discusses the intake of these various rodent carcinogen and mutagens from everyday foods in the diet of humans:

> *Our estimate of 1.5 g of natural pesticides per person per day is based on the content of toxins in the major plant foods (e.g., 13 g of roasted coffee per person per day contains about 765 mg of chlorogenic acid, neochlorogenic acid, caffeic acid, and caffeine; see refs. 22 and 23 and Table 2). Phenolics from other plants are estimated to contribute another several hundred milligrams of toxins. Flavonoids and glucosinolates account for several hundred milligrams; potato and tomato toxins may contribute another hundred, and saponins from legumes another hundred. Grains such as white flour and white rice contribute very little, but whole wheat, brown rice, and corn (maize) may contribute several hundred milligrams more. The percentage of a plant's weight that is toxin varies, but a few percent of dry weight is a reasonable estimate: e.g., 1.5% of alfalfa sprouts is canavanine and 4% of coffee beans is phenolics.*

Ames et al. (1990) estimated, based on the number of natural pesticides that have tested positive as rodent carcinogens, that it is probable that almost every fruit and vegetable at the grocery story contains natural plant pesticides that are rodent carcinogens. Ames et al. (1990) point out that caution is necessary when interpreting the implications of the

occurrence in the diet of natural pesticides that are rodent carcinogens. Ames et al. state that they are not arguing there is much relevance to human cancer, and they add that diets high in fruits and vegetables are associated with lower cancer rates, possibly due to anticarcinogenic vitamins and antioxidants gleaned from plants. These authors reiterate, "What is important in our analysis is that exposures to natural rodent carcinogens may cast doubt on the relevance of far lower levels of exposures to synthetic rodent carcinogens."

Table 11. Forty-nine natural pesticides and metabolites found in cabbage

Glucosinolates:
2-propenyl glucosinolate (sinigrin)*, 3-methylthiopropyl glucosinolate, 3-methylsulfinylpropyl glucosinolate, 3-butenyl glucosinolate, 2-hydroxy-3-butenyl glucosinolate, 4-methylsulfinylbutyl glucosinolate, 4-methylsulfonylbutyl glucosinolate, benzyl glucosinolate, 2-phenylethyl glucosinolate, propyl glucosinolate, butyl glucosinolate
Indole glucosinolate and related indoles:
3-indolylmethyl glucosinolate (glucobrassicin), 1-methoxy-3-indolylmethyl glucosinolate (neoglucobrassicin), **indole-3-carbinol***, indole-3-acetonitrile, bis(3-indolyl)methane
Isothiocyanates and goitrin:
allyl isothiocyanate*, 3-methylthiopropyl isothiocyanate, 3-methylsulfinylpropyl isothiocyanate, 3-butenyl isothiocyanate, 5-vinyloxazolidine-2-thione (goitrin), 4-methylthiobutyl isothiocyanate, 4-methylsulfinylbutyl isothiocyanate, 4-methylsulfonylbutyl isothiocyanate, 4-pentenyl isothiocyanate, benzyl isothiocyanate, phenylethyl isothiocyanate
Cyanides:
1-cyano-2,3-epithiopropane, 1-cyano-3,4-epithiobutane, 1-cyano-3,4-epithiopentane, *threo*--1-cyano-2-hydroxy-3,4-epitiobutane, *erythro*--1-cyano-2-hydroxy-3,4-epithiobutane, **2-phenylpropionitrile, allyl cyanide***, 1-cyano-2-hydroxy-3-butene, 1-cyano-3-methylsulfinylpropane, 1-cyano-4-methylsulfinylbutane
Terpenes:
menthol, neomenthol, isomenthol, **carvone***
Phenols:
2-methoxyphenol**, 3-caffoylquinic acid (chlorogenic acid)***, **4-caffoylquinic acid*, 5-caffoylquinic acid***, 4-(*p*-coumaroyl)quinic acid, 5-(*p*-coumaroyl)quinic acid, **5-feruloylquinic acid**

*Indicates data on mutagenicity or carcinogenicity (see Ames et al. 1990, for discussion of data); others untested. Also, chlorogenic acid's metabolite caffeic acid is mutagenic and carcinogenic. Indole-3-acetonitrile form a carcinogen in the presence of nitrite.

Adapted from Ames et al. (1990).

Table 12. Some natural pesticide carcinogens in food

Rodent Carcinogen	Conc. (ppm)	Plant Food
5-/8-Methoxypsoralen	14	Parsley
	32	Parsnip, cooked
	0.8	Celery
	6.2	Celery, new cultivar
	25	Celery, stressed
p-Hydrazinobenzoate	11	Mushrooms
Glutamyl *p*-hydrazinobenzoate	42	Mushrooms
Singrin*	35–590	Cabbage
	250–788	Collard greens
	12–66	Cauliflower
	110–1,560	Brussels sprouts
	16,000–72,000	Mustard greens
	4,500	Horseradish
d-Limonene	31	Orange juice
	40	Mango
	8,000	Pepper, black
Estragole	3,800	Basil
	3,000	Fennel
	3,000	Nutmeg
	10,000	Mace
	100	Pepper, black
Ethyl acrylate	0.07	Pineapple
Sesamol	75	Sesame seeds (heated oil)
a-Methylbenzyl alcohol	1.3	Cocoa
Benzyl acetate	82	Basil
	230	Jasmine tea
	15	Honey
Catechol	100	Coffee (roasted beans)
Caffeic acid	50–200	Apple, carrot, celery, cherry, eggplant, endive, grapes, lettuce, pear, plum, potato
	>1,000	Absinthe, anise, basil, caraway, dill, marjoram, rosemary, sage, savory, tarragon, thyme
	1,800	Coffee (roasted beans)
Chlorogenic acid[+] (caffeic acid)	50–500	Apricot, cherry, peach, plum
	21,600	Coffee (roasted beans)

Rodent Carcinogen	Conc. (ppm)	Plant Food
Neochlorogenic acid+ (caffeic acid)	50–500	Apple, apricot, broccoli, brussels sprouts, cabbage, cherry, kale, peach, pear, plum
	11,600	Coffee (roasted beans)

Adapted from Ames et al. (1990).

*Singrin is converted to allyl isothiocyanate and allyl cyanide, which are carcinogens.

+Chlorogenic and neochlorogenic acid are metabolized to the carcinogens caffeic acid and catechol but have not been tested for carcinogenicity themselves.

In addition, the National Research Council's (NRC's) Board of Environmental Studies and Toxicology Committee on Comparative Toxicity of Naturally Occurring Carcinogens published a conclusion similar to that of Ames (see pages 6 and 18, and Chapter 5, *Risk Comparisons*, in NRC, 1996). Although the committee admitted that more research was needed before definitive conclusions could be drawn, it stated that natural components of the diet were likely to be more significant with respect to cancer risk than synthetic chemicals found in food. The committee's conclusion was based on the amount of food consumed by the typical U.S. citizen and the levels of natural or synthetic pesticides present in those foods. The committee refers to various studies, including the National Health and Nutrition Examination Surveys (NHANES), the recent study of pesticides in the diets of infants and children, and the Nationwide Food Consumption survey performed by the U.S. Department of Agriculture (USDA), as sources of data for their analysis. The NRC committee concluded from these different studies that Americans consume a large number of natural and synthetic carcinogens in their diets. The committee also based its conclusion regarding the potential significance of dietary carcinogens on the fact that the natural dietary substances studied to date have, on average, a greater carcinogenic potency than the synthetic chemicals found in food.

Table 13 provides a partial list of natural chemicals found in foods categorized according to the scheme developed by the NRC. The NRC classified carcinogens in food as constitutive, derived, acquired, pass-through (accumulated from the plant or animal's environment), or added (those added during the food processing or food preparation stage; see Table 5-1 in NRC, 1996). "Constitutive" is the term used in the NRC report to designate the group of carcinogenic chemicals in food that are produced by plants and animals themselves. The NRC committee recognized that there is variability among the population with respect to the nature and doses of carcinogens consumed in food caused by differences in diet, variations in the chemicals produced by different strains of plants, and differences in the chemicals derived, acquired, passed through, or added to the food. Despite such variability, the NRC concluded that the diet is a significant source of carcinogens for all people due to the vast number of natural carcinogens found in foods and to the likelihood that only a relatively small number of natural chemicals produced by plants have actually been tested for carcinogenicity. Thus, with more study, an even larger number of natural carcinogens would likely be shown to be present.

Table 13. Naturally occurring carcinogens potentially present in U.S. diets

Constitutive:

Acetaldehyde, benzene, caffeic acid, cobalt, estradiol 17ß, estrone, ethyl acrylate, (with UV light exposure), 8-methoxypsoralen (xanthotoxin) (with UV light exposure), progesterone, safrole, styrene, testosterone

Derived:

A-alpha-C, acetaldehyde, benz(a)anthracene, benzene, benzo(a)pyrene, benzo(b) fluoranthene, benzo(j)fluoranthene, benzo(k)fluoranthene, dibenz(a,h)acridine, dibenz(a,j)acridine, dibenz(a,h) anthracene, formaldehyde, glu-P-1, glu-P-2, glycidaldehyde, IQ, Me-A-alpha-C, MeIQ, MeIQx, methylmercury compounds, N-methyl-N'-nitro-nitrosoquanidine, N-nitroso-N-dibutylamine, N-nitrosodiethylamine, N-nitrosodimethylamine, N-nitrosodi-N-propylamine, N-nitorosomehtylethylamine, N-nitrosopiperidine, N-nitrosopyrrolidine, N-nitrososarcosine, PhIP, Trp-P-1, Trp-P-2, urethane

Acquired:

Aflatoxin B_1, aflatoxin M_1, ochratoxin A. sterigmatocystin, toxins derived from *Fusarium moniliforme*

Pass through:

Arsenic, benz(a)anthracene, benzo(a)pyrene, beryllium, cadmium, chromium, cobalt, indeno(1,2,3)pyrene, lead, nickel[b]

Added:

Contaminant introduced through tap water: arsenic, asbestos, benzene, beryllium, cadmium, hexavalent chromium, dibenzo(a,l)pyrene, indenol(1,2,3,-cd)pyrene, radon

Indirect through use as drug or in packaging: i) veterinary drugs - estradiol 17ß, progesterone, reserpine, testosterone, ii) food-packaging material - benzene, cobalt, ethyl acrylate, formaldehyde, nickel

Direct food additives: acetaldehyde, ethyl acrylate, formaldehyde

Traditional foods and beverages: alcoholic beverages, betel quid, bracken fern, hot maté, pickled vegetables, salted fish (Chinese style)

Adapted from Table 5-1, NRC (1996).

NRC used the term "derived" to designate those carcinogenic chemicals that are produced when foods are cooked, stored, or preserved. Benzene, glycidaldehyde, heterocyclic amines, nitrosamines, and polycyclic aromatic hydrocarbons (PAHs) are the major chemicals and chemical classes that comprise the "derived" carcinogens. PAHs are produced when foods are cooked; hence, they are found in greatest concentrations in charred meats, smoked fish, vegetable oils, tea, and roasted coffee, and also in some fruits and vegetables. Several foods contain PAHs at concentrations in excess of ten parts per billion (see Table 14, adapted from Menzie et al., 1992, for levels of carcinogenic PAHs found in common foods and potential doses of PAHs from various sources). The actual number of PAHs consumed in the diet is highly variable and depends on both the composition of the diet and the methods of cooking used. Statistics developed by the USDA were used by Menzie et al. (1992) to estimate an average dietary intake of PAHs for U.S. males of approximately 3 µg per day (0.043 µg/kg/day).

Menzie et al. (1992) also compared potential doses of PAHs from various sources in addition to diet [adapted from Table 3 of (Menzie et al., 1992) and presented in Table 15] and concluded that smokers may incur doses of PAHs up to twice those of nonsmokers.

Interestingly, the intake of PAHs from food was estimated to be equal to that from tobacco smoke, indicating that PAH doses incurred by nonsmokers are within a factor of two of those received by active smokers from all sources combined.

Table 14. Levels of carcinogenic PAHs found in common foods

Food	Average Minimum Level (ppb)	Average Maximum Level (ppb)
Non-charcoal broiled	0.11	0.69
Charcoal-broiled foods		
Beef	26	35
Pork	12	26
Poultry	12	12
Frankfurters/sausage	8	12
Fish/shellfish	0.1	0.1
Smoked fish/shellfish	9	36
Vegetables (tomatoes, potatoes, green leafy)	1-19	1–46
Grains	0.6	9
Fruits	0.5	2.4
Nonalcoholic beverages	2	27
Alcoholic beverages	0.04	0.08
Fats & oils	3.4	66
Cheese	1.7	1.7

Adapted from Menzie et al. (1992).

Table 15. Potential doses of PAHs from various sources

	Median Values		Maximum Values	
Source of PAHs	**Intake (µg/day)**	**Percent of Total**	**Intake (µg/day)**	**Percent of Total**
Food	3	96.2	12	79
Air	0.05	1.6	2.70	18
Water	0.006	0.2	0.124	1
Soil	0.06	1.9	0.4	2
Total	3.12	100	15.22	100
Mainstream Smoke	2–5 (1 pack/day)		6–15 (3 packs/day)	
	3		15	
Total	5–8		21–30	

Adapted from Menzie et al. (1992).

Heterocyclic amines are formed from the reaction of amino acids with creatinine, both of which are abundant in meat. The amounts formed are most dependent on high cooking temperatures, but longer cooking times also increase formation. Heterocyclic amines are present in many cooked meats and fish. They have produced tumors in numerous tissues in both rodent and monkey cancer bioassays (see Wakabayashi et al., 1992, and Adamson and Thorgiersson, 1995, for information on rodent carcinogens of heterocyclic amines and amounts of heterocyclic amines in cooked foods). Table 16 lists rodent carcinogenicity data of several heterocyclic amines.

Table 16. Rodent carcinogenicity of heterocyclic amines

Heterocyclic Amine (Abbreviation)	Tumor Sites in Animals
2-Amino-3-methylimidazo[4,5-*f*]quinolone (IQ)	Liver, lung, forestomach, small & large intestines, Zymbal gland, clitoral gland, and skin
2-Amino-3,4-dimethylimidazo[4,5-*f*]quinolone (MeIQ)	Liver, forestomach, large intestine, Zymbal gland, skin, oral cavity, and mammary gland
2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx)	Liver, lung, hematopoietic system, Zymbal gland, clitoral gland, and skin
2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP)	Large intestine, mammary gland, lymphoid tissue
3-amino-1,4-dimethyl-5H-pyrido[4.3-*b*]indole (Trp-P-1)	Liver
3-amino-1-methyl-5H-pyrido[4.3-*b*]indole (Trp-P-2)	Liver

Heterocyclic Amine (Abbreviation)	Tumor Sites in Animals
2-amino-6-methyldipyrido[1,2-a:3',2'-*d*]imidazole (Glu-P-1)	Liver, small & large intestines, Zymbal gland, clitoral gland, and blood vessels
2-aminodipyrido[1,2-a:3',2'-*d*]imidazole (Glu-P-2)	Liver, small & large intestines, Zymbal gland, clitoral gland, and blood vessels
2-amino-9*H*-pyrido[2,3-*b*]indole (AaC)	Liver, blood vessels
2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole (MeAaC)	Liver, blood vessels

Adapted from Wakabayashi et al. (1992).

"Acquired" carcinogenic food contaminants consist of those naturally occurring carcinogens that are absorbed by food organisms from their environment. These include the heavy metals (e.g., arsenic or lead) and potent mycotoxins released by molds (e.g., aflatoxin, ochratoxin, etc.). Using results from an FDA survey, it is estimated that the average daily intake of the known human carcinogen aflatoxin B_1 from corn and peanut products is about 16.8 ng. Daily intakes of carcinogenic Fumonisin B_1 are estimated to be in the range of 2 to 40 ng/kg/day.

Daily doses of "Pass-Through" and "Added" carcinogens are highly variable and depend on the location of crop or livestock production and on handling, storage, and processing of the food. PAHs and inorganic metals are two of the most common "pass-through" carcinogens in foods. Intentional Food Additives include caloric sweeteners, acidifiers, spices and herbs, essential oils, and the major synthetic flavors. These will not be discussed in detail here, because the variability in levels found in typical foodstuffs leads to difficulty in estimating daily intakes of these chemicals from foods.

A review of various literature sources provides a list of naturally occurring carcinogens in food (see Table 17).

Table 17. Natural chemicals found in the diet that are carcinogenic to rodents

Chemical name	Source*
3,4-Dihydrocoumarin	Food additive for non-alcoholic beverages, ice cream, ices, candy, baked goods, gelatins, puddings, chewing gum
4-Methylcatechol	Coffee
8-Methoxypsoralen	Celery, parsnip, parsley
Acetaldehyde	Coffee, bread, apple pie, apples, grapes, mangos, meat, pears, pineapple, tomatoes
Acetaldehyde methylformylhydrazone	Several species of edible mushrooms, especially the genus *Gyromitra*
Acrylamide	Bread, rolls
Aflatoxin B_1	Corn, grains, cereal, peanuts/peanut butter, nuts, coconut, milk,

Chemical name	Source*
Aflatoxin, crude	Nuts
Allyl isothiocyanate	Cabbage, broccoli, horseradish, black mustard seed/mustard, arugula
Benzaldehyde	Found in over 40 foods; fruits and vegetables; white bread, wine, coffee, tea, shellfish
Benzene	Coffee, butter, roast beef
Benzo(*a*)pyrene	Margarine, coconut oil, broiled meat, broiled fish, smoked fish, ham, bacon, cereal, potatoes, flour, bread/toast, lettuce, tomatoes, spinach, fruits, roasted coffee, tea, whiskey
Benzofuran	Coffee
Benzyl acetate	Jasmine tea
Cadmium chloride	Shellfish, liver, kidney meats
Caffeic acid	Apples, apple pie, carrot, celery, citrus, lettuce/green salad, peach, pear, plum, grapes, mango, pineapple, potato, tomato, coffee
Capsaicin	Hot chili peppers
Catechol	Coffee
Coumarin	Cinnamon
Crotonaldehyde	Mussels
Dibenz(*a,h*)anthracene, Formaldehyde, Hydroquinone & Isoprene	Coffee
d-Limonene	Citrus juices, citrus oils, apples, grapes, mangos, pears, pineapple, other fruits and vegetables, coffee, tea, spices, nutmeg
Estragole	Apple, apple pie, bilberry, basil, oregano, tarragon, anise, star anise, fennel
Ethyl acrylate	Dill, pineapple, raspberry, durian, apples, grapes, mangos, pears
Ethyl alcohol	Bread, red wine, white wine, rolls, tomatoes
Ethyl benzene	Coffee
Ethyl carbamate	Bread, rolls, red wine
Furan and derivatives	Bread, onions, celery, mushrooms, sweet potatoes, rolls, cranberry sauce, coffee
Furfural	Cocoa, coffee, wine, whiskies, cider, sherry, beer, sauerkraut, tomato, cinnamon, cloves, bread, many fruits, mixed roasted nuts, sweet potatoes
Glu-P-1 and Glu-P-2	Broiled fish, grilled meats, fresh juices from vegetables and fruits (e.g., cabbage, pepper, eggplant, apple, burdock, stone-leek, ginger, mint leaf, pineapple)
Heterocyclic amines	Roast beef, turkey
Hydrazines	Mushrooms
Hydrogen peroxide	Coffee, tomatoes
Hydroquinone	Coffee
d-Limonene	Black pepper, mangoes
IQ	Fried ground beef/hamburger, broiled beef, sun-dried broiled sardines, broiled salmon, fried fish, fried egg

Chemical name	Source*
MeA-α-C acetate	Broiled fish, grilled meats, fresh juices from vegetables and fruits (e.g,. cabbage, pepper, eggplant, apple, stone-leek, ginger, pineapple)
MeIQ	Fried fish, grilled/sun-dried sardines, broiled sardines
MeIQx	Fried ground beef/hamburger, broiled beef, fried fish, broiled mutton, broiled salmon, dried/smoked mackerel, broiled chicken, roasted eel
4-Methylcatechol	Coffee
Methylhydrazine	Mushrooms
Methyl eugenol	Basil, cinnamon, nutmeg
Monocrotaline	Crotalaria species of bush teas
*N*2-γ-Glutamyl-*p*-hydrazinobenzoic acid	Edible mushrooms
Nitrosodibutylamine	Soybean oil, cheese, pork luncheon meat, salami-like sausages, cooked and smoked ham, bacon-like products, fried salted yellow croaker
N-Methyl-*N*-formylhydrazine	Edible false morel mushroom
N-Nitrosodiethylamine	Canned luncheon meats, cured meats, cooking oils, butter, margarine, fried salted yellow croaker, steamed salted yellow croaker, beer
N-Nitrosodimethylamine	Cheese, soybean oil, canned fruit, various meat products, bacon, various cured meats, frankfurters, cooked ham, fish, spices for meat curing, apply brandy, alcoholic beverages, beer
N-Nitrosodipropylamine	Cured meats, cheese, salt-preserved fish, alcoholic beverages
N-Nitrosopiperidine	Cheeses, smoked cod, fried smoked back rashers, sausage, bologna, wieners, meatloaf, various processed and preserved meats, bacon
N-Nitrosopyrrolidine	Fried bacon, Cured beef and pork, fried ham, sausage, cheese, salami, canned pork with jelly, luncheon meats, smoked cod, smoked kippers
Ochratoxin A	Cereals, wines, grape juice, coffee
PhIP HCL	Fried ground beef/hamburger, broiled chicken, fried fish,
p-Hydrazinobenzoic acid HCL	Several species of edible mushrooms, especially the genus *Gyromitra*
Psoralens	Celery, parsley
Quercetin	Ubiquitous in food plants, rinds of fruits, bread stuffing, apple pie, apples, grapes, mangos, pears, pineapple, tomatoes, onions, tea
Safrole	Cocoa, nutmeg, black pepper, bread stuffing, nutmeg
Sterigmatocystin	Cereals, grain products, bread, fruits, marmalade, dried meat products, grapefruit juice, cured ham, salami
Styrene	Nuts, whisky, yogurt, butter-fat cream, butter, margarine, cottage cheese, sour cream, homogenized milk, honey, cinnamon, plums, nectarines, grapes, scrambled eggs, sandwich cookies, cake donuts, soybean curds, salt-fermented fish and shrimp pastes
Symphytine	Comfrey-pepsin tablets; comfrey herb tea

Chemical name	Source*
Trp-P-1 acetate, Trp-P-2 acetate	Charred cooked fish and meat, fresh juices from vegetables and fruits (e.g., cabbage, pepper, eggplant, apple, ginger, mint leaf, pineapple)
Urethane	All fermented and yeast-leavened foods, wine, yogurt, soy sauce, sake, liquors, ale, beer, bread/toast
α-Ecdysone	Spinach, crustaceans
α-Methylbenzyl alcohol	Flavoring agent in various foods

* Sources: Natural pesticides from Table 2 of Ames and Gold chapter.

Naturally occurring animal and human carcinogens that might be present in U.S. human diets (from Table 5.1 of *Carcinogens and Anticarcinogens in the Human Diet*).

Selected substances in food with some degree of animal positivity (Appendix A of *Carcinogens and Anticarcinogens in the Human Diet*).

American Council on Science and Health *Holiday Dinner Menu* printout.

The Carcinogenic Potency Database (CPDB). 2004. Summary Table of the Carcinogenic Potency Database by Chemical. http://potency.berkeley.edu/pdfs/ChemicalTable.pdf.

Johnson (2002) evaluated the number of food additives in the FDA's Everything Added to Food database (EAFUS, that contained 3,125 agents), combined with the National Toxicology Program's (NTP's) list of chemicals tested. Johnson (2002) determined that 43% of food additives had tested positive for carcinogenicity. Johnson (2002) stated, *"If this percentage is extrapolated to all substances added to food in the United States, it would imply that more than 1000 of such substances are potential rodent carcinogens."*

The excess theoretical cancer risk from exposure to carcinogens in the diet alone has been estimated to be on the order of 2.2×10^{-3} to 7.7×10^{-2} (2.2 in 1,000 to 7.7 in 100) or higher depending upon what chemical carcinogens are included in the analysis (NRC, 1996; Scheuplein, 1992) (Table 18). Scheuplein (1992) estimates the daily intake of carcinogens in food at approximately 1,012.3 mg per day. The risk from naturally occurring carcinogens is about 10,000 times higher than the risk posed by synthetic pesticides and contaminants. This was also stated by Gold et al. (2002):

> *On average, Americans ingest roughly 5,000 to 10,000 different natural pesticides and their breakdown products. Americans eat about 1,500 mg of natural pesticides per person per day, which is about 10,000 times more than they consume of synthetic pesticide residues.*

Table 18. Risk estimates of various food categories containing carcinogenic substances

Food Category	Amount of Food	Amount of Carcinogen (Estimated)	Excess Cancer Risk
Traditional food	1000 g	x 0.1% = 1000 mg	7.61×10^{-2}
Spices and flavors	1 g	x 1% = 10 mg	7.61×10^{-4}
Indirect additives	20 mg	x 10% = 2 mg	1.52×10^{-4}
Pesticides and contaminants	200 µg	x 50% = 0.1 mg	7.61×10^{-6}
Animal drugs	1 mg	x 10% = 0.1 mg	7.61×10^{-6}
Cooking (charred protein only)	1 g	x 0.01% = 0.1 mg	7.61×10^{-6}
Mycotoxins	10 µg	x 10% = 0.001 mg	7.61×10^{-8}
		Total risk	7.7×10^{-2}

Source: Table 9 from Scheuplein (1992).

Archibald and Winter (1990) estimated cancer risks associated with pesticide residues on food, and these results are presented in Table 19.

Table 19. Cancer risks associated with ingesting pesticide-contaminated foods, according to the National Research Council*

Food Source	Lifetime Cancer Risk**
Apples	3.23×10^{-4}
Beef	6.49×10^{-4}
Lettuce	3.44×10^{-4}
Oranges	3.76×10^{-4}
Peaches	3.23×10^{-4}
Pork	2.67×10^{-4}
Potatoes	5.21×10^{-4}
Tomatoes	8.75×10^{-4}
Wheat	1.92×10^{-4}
Soybeans	1.28×10^{-4}
Beans	1.23×10^{-4}
Carrots	1.22×10^{-4}
Chicken	1.12×10^{-4}
Corn (bran, grain)	1.09×10^{-4}
Grapes	1.09×10^{-4}

*Source: Archibald and Winter (1990).

**These upper-bound estimates are derived using EPA data and methods. They assume that residues are at the tolerance levels.

5.1.9.6 Background Exposures to Carcinogens in Drinking Water

The Safe Drinking Water Act of 1980 and the Safe Drinking Water Amendments regulate drinking water in the United States. One provision of these laws places limits on the concentrations of chemical contaminants that can legally be present in the drinking-water supply. These laws were spurred in part by the recognition that numerous chemicals are present in drinking water as a result of both industrial and residential activities. For example, in 1977, the National Academy of Sciences published a book titled, *Drinking Water and Health* (NRC, 1977) in which it identified some 298 different chemicals as having been detected in drinking water to that date. Today, that number is likely to have increased due to advancements in the analytical techniques available to detect chemicals.

Although many of the chemicals in drinking water are common chemicals that pose little or no risk to public health, some of the chemicals in our drinking water are carcinogens. Not all of these carcinogenic chemicals are present in all drinking water. However, much of the drinking water in the United States is disinfected by the addition of chlorine compounds. Chemical reactions that normally occur in water then produce chlorinated organic compounds as a result of these disinfection techniques, as well as a number of other

disinfection by-products, from their reaction with organic and inorganic matter in the water. In fact, several hundred disinfection by-products have been detected in water treated with various disinfectants (e.g., chlorine, chloramine, and ozone) to date (Woo et al., 2002).

Chlorinated methanes and chlorinated acetic acids, as well as several other chlorinated organic compounds formed in drinking water, are carcinogenic, at least in animal cancer bioassays. Below is a list of the cancer classifications of various disinfectants and disinfection by-products.

One of the major classes of carcinogenic disinfection by-products is the trihalomethanes (chloroform, bromoform, dibromochloromethane, bromodichloromethane, etc.). The EPA has set a limit of 80 ppb on levels of trihalomethanes in finished drinking water (EPA, 2021). The EPA (2021) lists the potential health effects from these compounds as liver, kidney, or central nervous system problems, along with an increased risk of cancer. These chemicals are typically present in every chlorinated drinking water supply in the United States.

Another class of disinfection by-products that contain some carcinogenic agents is the haloacetic acids. The EPA has set the MCL for five haloacetic acids (monochloro-, dichloro-, trichloro-, bromo-, and dibromoacetic acids) at 60 ppb (EPA, 2021) based on a concern for an increased risk of cancer. Dichloroacetic acid has also been used as an ingredient in pharmaceuticals, as a pesticide, and as a topical astringent (EPA, 1994). Trichloroacetic acid has been used as an herbicide, and also has been used medically as a chemical peeling agent for damaged skin, cervical dysplasia, and tattoo removal (EPA, 1994).

Krasner et al. (1989) gathered data on concentrations of various disinfection by-products from 35 water treatment facilities in the United States. Trihalomethanes and haloacetic acids were the compounds detected in the highest concentrations. Total trihalomethane concentrations ranged from 30 to 44 ppb, and total haloacid compounds ranged from 13 to 21 ppb. The EPA (1994) proposed rule for drinking-water disinfectants also provides data on concentrations of various disinfectants and disinfection byproducts in drinking water. Chloroform has been detected at levels ranging from <0.2 to 430 ppb (EPA, 1994). Bromodichloromethane, bromoform, dichloroacetic acid, and trichloroacetic acid have been detected in ranges of <0.2–110 ppb, <0.2–110 ppb, <0.4–75 ppb, <0.4–77 ppb, respectively (EPA, 1994). Chloral hydrate [an EPA Group C (possible) carcinogen] has been detected at levels ranging from <0.2 to 30 ppb (EPA, 1994). IARC (2004) reported levels of dichloroacetic acid in drinking water in the United States ranging from 0.33 to 133 ppb. Trichloroacetic acid levels in drinking water in the United States, as reported by IARC (2004), ranged from 0.25 to 170 ppb. Norwood et al. (1985) reported levels of trichloroacetic acid (TCAA) in municipal drinking water for several U.S. cities; TCAA concentrations ranged from 3.2 to 56.0 μg/L (ppb).

Calafat et al. (2003) recently measured urinary TCAA levels in the urine of 402 adults as part of the NHANES III sampling. The geometric mean was 2.9 μg/L (ppb) TCAA, and the 90^{th} percentile was 23 μg/L. A few individuals had urinary TCAA levels >100 μg/L. Urban males and females had higher mean TCAA urine levels (5.3 μg/L and 2.9 μg/L,

respectively) compared to rural subjects (2.2 μg/L and 2.6 μg/L, respectively), due to the fact that urban residents are more likely to use chlorinated water.

Bromate is a concern in water purification plants that use ozone and chlorine dioxide (Woo et al., 2002). The EPA MCL for bromate (EPA B2 carcinogen) is 10 ppb (EPA, 2009). Bromate has been detected in drinking-water samples at levels up to 90 ppb (EPA, 1994). Another disinfection by-product that has been shown to be carcinogenic in animals is 3-chloro-4-dichloromethyl-5-hydroxy-2(5H)-furanone or MX. MX was evaluated by IARC (2004) and classified as a Group 2B carcinogen and is considered a potent, direct-acting mutagen. MX has been detected at fairly low levels in drinking water in the United States (Wright et al., 2002; IARC, 2004). In one study conducted on Massachusetts' drinking water, it was reported that MX accounted for up to 63% of the mutagenic activity in drinking water (Wright et al., 2002).

The "average" dose of carcinogens for a U.S. citizen whose drinking water comes from the public water supply varies, because both the classes of organic chemicals present in drinking water before it is chlorinated and their concentrations in the water vary with geographic location. Nonetheless, one may calculate the "average" dosage of various carcinogens allowed to be in drinking-water supplies, according to the EPA risk assessment techniques by assuming a consumption rate of 2 liters per day. Chemicals are present at MCL concentrations or some percentage thereof. Of course, normal home activities like bathing, cooking, and cleaning provide additional routes of exposure to these compounds, and so contribute to the total risk associated with exposure to drinking water.

5.1.9.7 Background Exposures to Carcinogens in Air

In addition to consumption of carcinogens in water and in food, we all breathe carcinogenic chemicals daily. Several studies have measured the levels of airborne carcinogenic contaminants typically found in indoor environments. The sources of these carcinogenic air contaminants include cigarette smoke, wood-burning stoves, gas stoves and other gas appliances, building materials, home cleaning supplies, and other products used in and around the home (e.g., carpet shampoo, cooking and heating fuels, aerosol propellants, cleaning compounds, refrigerants, lubricants, flavoring agents, perfume base, fumigants, pesticides, dry cleaning solvents, tap water, transformers, plastics, paints, varnishes, glues, paint thinners, cosmetics, paper products, cardboard, and particle board), and gasoline exhaust emissions infiltrating into the home from the garage.

Since 1979, the EPA has been engaged in a series of studies designed to measure ambient (background) exposure levels to chemicals found in outdoor and indoor air (Wallace et al., 1986). Three groups of pollutants have been studied: volatile organic compounds (VOCs), carbon monoxide, and pesticides. These studies were carried out in roughly 12 U.S. cities and involved more than 2,000 participants. Because the EPA used a strict probabilistic sampling procedure, these studies probably represent a population as large as 3 million U.S. citizens (Wallace, 1989a). The studies were generally referred to as the TEAM studies (Total Exposure Assessment Methodology studies), and the results of various portions of the TEAM studies have been published (Pelizarri et al., 1986; Wallace et al., 1986, 1987, 1988; Wallace, 1989a,b; Wallace, 1991a,b; Thomas et al., 1993).

One of the publications (Wallace, 1991a) provides a concise summary of the results of the TEAM studies, and it is on this summary that the following discussion is based. Wallace (1991a) published indoor exposure levels for 12 volatile organic chemicals, 7 termiticides, and 16 pesticides/herbicides. Using the exposure levels published by Wallace, lifetime average daily doses of these chemicals were calculated, and these figures are presented in Tables 20 and 21.

Table 20. Indoor air exposures to VOCs (TEAM studies)

Chemical	Indoor Exposure Levels ($\mu g/m^3$)	Lifetime Average daily Dosage† (ng/kg/day)
Benzene Air Smokers	 15 90	 4,285.7 25,714.3
Vinylidene chloride	6.5	1,857.1
Chloroform Air Showers (inhalation) Water Food/beverages	 3 2 30 30	 857.1 571.4 8,571.4 8,571.4
p-Dichlorobenzene	22	6,285.7
1,2-Dibromoethane	0.05	14.3
Methylene chloride	6	1,724.3
Carbon tetrachloride	1	285.7
Tetrachloroethylene	15	4,285.7
Trichloroethylene	7	2,000.0
Styrene Air Smokers	 1 6	 285.7 1,714.3
1,2-Dichloroethane	0.5	142.9
1,1,1-Trichlorethane	30	8,571.4

Adapted from Wallace (1991a)

† Lifetime dosages were computed in the following manner: air concentration times 20 m^3 of air inhaled per day and divided by an adult body weight of 70 kg. (Note: 1 μg = 1,000 ng).

Table 21. Household exposures to pesticides (TEAM studies)

Pesticide	Exposure (ng/m^3)†	Lifetime Average Daily Dosage (ng/kg/day)§
Banned termiticides		
Heptachlor	71	20.3
Chlordane	198	56.6
Aldrin	13	3.74
Dieldrin	3	0.86
Heptachlor epoxide	0.4	0.11
DDE	2.2	0.63
DDT	0.7	0.20
Other pesticides		
Dichlorvos	33	9.4
g-BHC (lindane)	6.6	1.89
a-BHC	0.5	0.14
Propoxur	100	28.6
Hexachlorobenzene	0.3	0.086
Dicofol	2.6	0.74
o-Phenylphenol	58	16.6
2,4-D	0.6	0.17
Atrazine	0.05	0.014
cis-Permethrin	0.4	0.11
trans-Permethrin	0.1	0.029
Chlorothalonil	0.7	0.20
Folpet	0.5	0.143
Captan	0.1	0.029
DDD	<4	<1.14
Pentachlorophenol	<730	<208.6

† Adapted from Wallace, L.A. 1991a.

§ Lifetime dosages were computed in the following manner: air concentration times 20 m^3 of air inhaled per day and divided by an adult body weight of 70 kg.

The results of the TEAM studies indicate that indoor air is a significant confounding source of potentially carcinogenic chemicals common to everyone. Based on the average daily doses that can be calculated based on the TEAM study measurement, one interesting feature of Table 22 that stands out is that the single greatest source of carcinogenic VOCs (benzene) is mainstream tobacco smoke (the smoke inhaled by smokers). In addition to benzene inhaled by active smokers, a number of publications have discussed the doses of carcinogenic smoke constituents inhaled by nonsmokers exposed to environmental tobacco smoke. Repace and Lowrey (1990) have summarized and interpreted some of the available exposure, dose-response, and risk estimates for nonsmokers exposed to environmental tobacco smoke. Using either the best biological marker (cotinine) or the best atmospheric marker (respirable suspended particulates) of exposure to tobacco-smoke components, Repace and Lowrey (1990) estimated the average exposure of nonsmokers to be 0.5% to 1.0% that of smokers.

5.1.9.8 Cancer Risks from Diagnostic Medical Procedures

The FDA has commented on the dose of radiation and excess cancer risk associated with receiving a CT scan, pointing out that the amount of radiation from a CT scan with 10 mSv

(or about 1,000 mrem) of radiation dose carries with it an excess risk of fatal cancer of about 1 chance in 2,000, or about 5 x 10^{-4} (FDA, 2017). Interestingly, the FDA states that the effective doses from diagnostic CT procedures are in the range of 1 to 10 mSv. This range is not much less than the lowest doses of 5 to 20 mSv received by some of the Japanese survivors of the atomic bombs, individuals who had small but increased radiation-related excess relative risks for *cancer mortality* (FDA, 2017). Excess cancer risk associated with various diagnostic procedures and treatments are provided in Table 22. Excess cancer risks from the various medical diagnostic procedures listed in Table 22 are fairly high and can exceed 1 x 10^{-4} (e.g., lower back x-rays, barium enema, upper GI, bone scan, head CT scan) or 1 x 10^{-3} (e.g., for coronary angioplasty).

Table 22. Excess cancer risks associated with various medical diagnostic procedures and treatments

Procedure	Radiation Dose (mSv)	Excess Cancer Risk per Procedure*	Reference for Radiation Dose Amount
Chest x-ray	0.16	1.6 x 10^{-5}	Brenner and Hall (2007)
Single lateral L-spine x-ray (avg. male & female)	0.68	6.8 x 10^{-5}	Hall (2000)
Bilateral mammogram	0.8	7.6 x 10^{-5}	ASRT (2018)
Lower back x-rays	1.5	1.7 x 10^{-4}	ASRT (2018)
Brain CT	2	2.3 x 10^{-4}	ASRT (2018)
Chest CT	7	8 x 10^{-4}	ASRT (2018)
Bone scan	4.2	4.2 x 10^{-4}	Finestone et al. (2003)
Intravenous urogram	4.4	4.4 x 10^{-4}	Hall (2000)
Average PET scan	3.9	3.9 x 10^{-4}	Hall (2000)
Upper GI (Barium swallow)	6.0	6.9 x 10^{-4}	ASRT (2018)
Barium enema	8	8 x 10^{-4}	Holmes (2011)
Liver angiography	21.7	2.2 x 10^{-3}	Hall (2000)
Head-neck angiography	5	5 x 10^{-4}	Mettler et al. (2008)
Virtual colonoscopy CT	10	9 x 10^{-4}	ASRT (2018)
Abdominal CT scan	10	1 x 10^{-3}	Brenner and Hall (2007)
Coronary angiography	12	1.2 x 10^{-3}	Hall (2000)
Whole body PET/CT scan	14.1	1.6 x 10^{-3}	ASRT (2018)
Coronary angioplasty	22	2.2 x 10^{-3}	Hall (2000)
Cardiac stress-rest test (thallium)	40.7	4 x 10^{-3}	Mettler et al. (2008)
Pelvic vein embolization	60.0	5.7 x 10^{-3}	ASRT (2018)

* Calculated using 1 x 10^{-4} risk per mSv (BEIR VII, 2006) or online calculator (ASRT, 2018).

Benke (1995) also provided risks of developing cancer over a lifetime for males and females (Table 23). For instance, a 10-year-old boy who is given a full-mouth dental x-ray has a 1-in-600 chance (1.7 x 10^{-3}) of developing cancer later.

Table 23. Risk of common x-ray exams tabulated as the chance of developing cancer over a lifetime

Exam	Age	Male	Female
		One chance in:	
Chest (2 exp.)	Newborn	3,500	1,800
	10	6,000	4,200
	40	59,000	28,000
	50	1,400,000	630,000
Lower arm (2 exp.)	5	300,000	350,000
Angiocardiography (40 exp. + 30 min. fluoroscopy)	5	120	80
	40	800	500
Full mouth (16 exp.)	5	600	1,300
	10	600	1,400
	40	2,400	6,100
Full spine (1 exp.) (chiropractic)	5	570	360
	10	500	300
	40	2,500	1,600
Mammography (2 exp.)	20		550
	30		600
	40		1,400
	50		32,200

Source: Benke, K.K. (1995).

As mentioned, we all receive a background dose of radiation each day that represents an additional source of excess cancer risk. The average background dose of radiation to individuals in the United States is 620 mrem per year. This includes radiation from background exposures (310 mrem; radon in air, cosmic rays, etc.[10]) and man-made sources

[10] Radiation from sun and stars, radioactive materials from soil and rock (e.g., radon and potassium), internal radiation (e.g., potassium-14 and carbon-14).

(310 mrem; medical, commercial, and industrial sources[11]) (see Figure 9 below). The estimated lifetime excess cancer risk from background radiation exposure we all experience of 360 mrem/year is about 1 x 10^{-2} or 1 in 100.

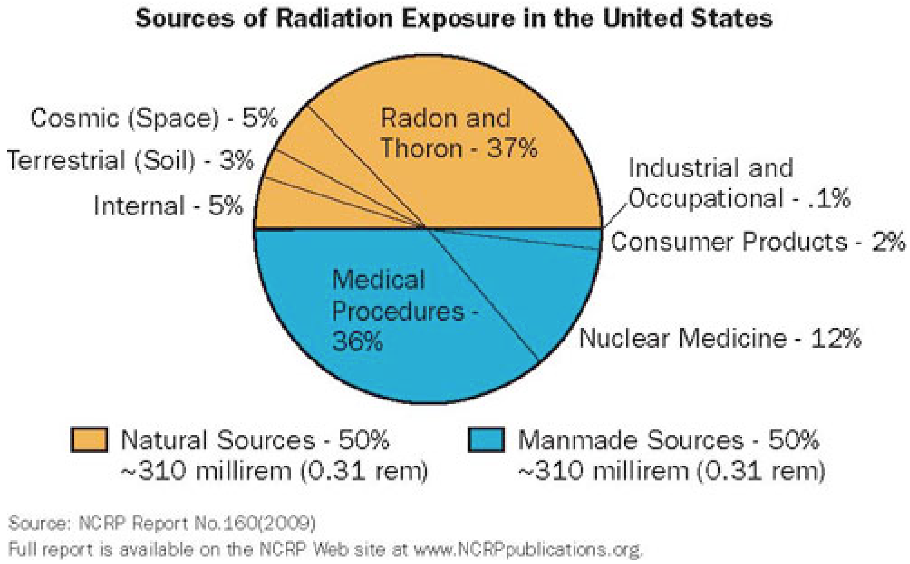


Figure 9. Sources of radiation
Source: NRC. 2020. https://www.nrc.gov/about-nrc/radiation/around-us/sources.html.

Humans also contain natural radioactivity, with about 0.01% of our body's potassium consisting of radioactive potassium-40 (Alazraki and Mishkin, 1988). Wilson and Crouch (2001) state that the excess annual risk from potassium-40 normally in the body is 1 in 100,000; so, for an individual living 70 years, lifetime excess risk would be about 1 in 1,400.

5.1.9.9 Background Risks Associated with Commonplace Activities

Wilson (1980) has evaluated the yearly risk of death associated with daily living. Table 24 presents cancer risks for common daily activities, in addition to those discussed in previous sections of this report. Table 25 shows the lifetime risk of death from various causes. These risks provide a context within which background risks discussed in this report and risks allegedly associated with exposure to NDMA or NDEA from valsartan can be interpreted.

[11] Diagnostic and nuclear medicine procedures, building and road construction materials, televisions, smoke detectors, luminous watches, tobacco, ophthalmic glass used in eyeglasses, etc.

Table 24. Cancer risks common to our daily activities*†

Activity	Lifetime Cancer Risk ($x 10^{-4}$)
Tobacco (smoker)	
all risks (includes heart disease)	2,100
cancer only	840
person in room with smoker	7
Air Pollution	
sulfates§	105
benzo[a]pyrene	21
Eating and Drinking	
cirrhosis (moderate drinker)§	28
4 tbsp. peanut butter/day (aflatoxin)	28
1 beer/day	14
1 pint milk/day (aflatoxin)	7
1/2 lb charbroiled steak/week	0.3
Contraceptive pills	14
Radiation Risks	
natural radiation at sea level	10.5
average medical x-ray	7
living in brick house£ vs. living in wood house	3.5
Cosmic Ray Risks	
frequent flyer	10.5
living in Denver vs. New York	7

*–Source: Wilson (1980).

†–Assumes a 70-year lifetime. §–Risks other than cancer. £–With radioactive bricks.

Table 25. Lifetime risk of death from selected causes

Activity or Disease	Lifetime Risk of Death
Heart disease	1.7×10^{-1}
Stroke	4.2×10^{-2}
Chronic lower respiratory disease	3.8×10^{-2}
Stroke	2.6×10^{-2}
Hospital infections	2.6×10^{-2}
Flu	1.6×10^{-2}
MRSA (resistant bacteria)	5.1×10^{-3}
Accidental poisoning	5.2×10^{-3}
Lightning	5.5×10^{-6}

Source: Florida Museum (2018); National Safety Council (2021).

5.1.9.10 Risks from Background Exposure to Radiation

5.1.9.10.1 Radon

Radon-222 (or radon) is a radioactive gas that forms naturally when uranium, thorium, or radium—radioactive metals—break down in rocks, soil, and groundwater. It is ubiquitous. We are always exposed to radon, because it occurs naturally from the earth. People can be exposed to radon in air from cracks and gaps in buildings and homes or in drinking water. The EPA states that there is no known safe exposure level for radon. The EPA's action level for radon in air is 4 pCi/L[12] (picocurie per liter). Further, the EPA recommends that Americans consider fixing homes that contain radon between 2 and 4 pCi/L (EPA, 2020a). Figure 10 below shows the general radon levels in the United States grouped into three zones. For example, Maine has radon air concentrations in Zones 1 and 2, but actual indoor air concentrations ranged up to 103.2 pCi/L (EPA, 1993).

[12] The level at which the EPA recommends one takes action to reduce a home's indoor radon concentration.

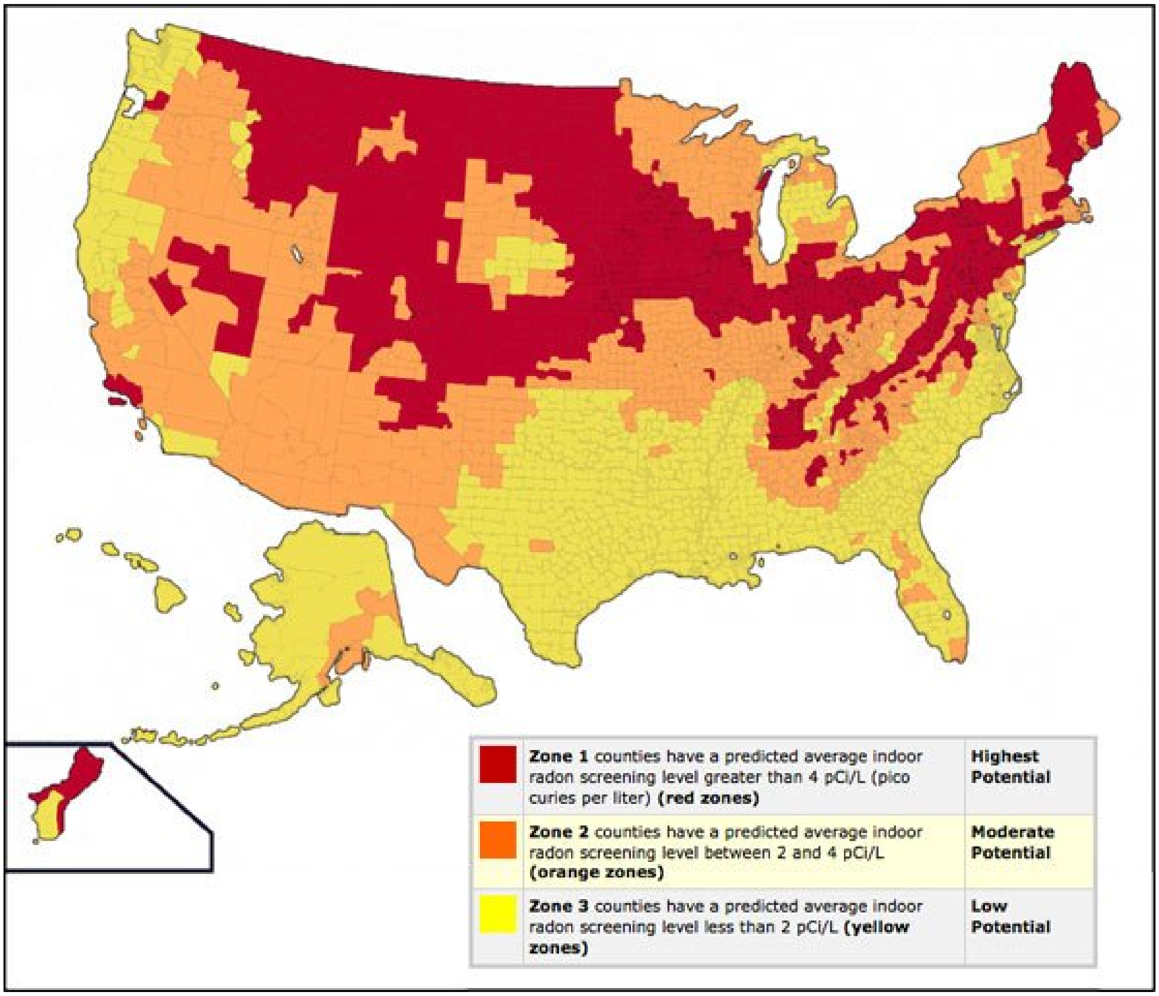


Figure 10. Radon levels in the United States
Source: EPA (2019).

According to EPA estimates, radon is the second-most common cause of lung cancer among Americans and is the leading cause of lung cancer among non-smokers. Radon is estimated to cause approximately 21,000 lung cancers per year in the United States, with smokers being at the highest risk of radon-induced lung cancer. Table 26 shows the excess risk of developing lung cancer among smokers and non-smokers, based on the lifetime air radon concentration to which an individual is exposed (EPA, 2020b). Based on the data for exposure to radon in air in the home, the excess cancer risk for lung cancer among non-smokers can range from ~2 in 1,000 (2×10^{-3}) to ~40 in 100 (4×10^{-1}) and from ~2 in 100 (2×10^{-2}) to ~3 in 10 (3×10^{-2}) for smokers, depending on the level of radon in the home. Note that lung cancer is one of the cancers that plaintiffs are alleging is associated with the use of valsartan; thus, radon should be considered as an alternative cause to any current or future case of lung cancer.

Table 26. Excess lung cancer risk associated with lifetime radon exposure for smokers and non-smokers

Indoor Air Radon Concentration	Smoking Status	The number of people out of 1,000 who could get lung cancer if they were exposed to this level over a lifetime...	The excess lung cancer risk is equal to...
1.3 pCi/L	Non-Smoker	~2 people	2×10^{-3}
"	Smoker	~20 people	2.0×10^{-2}
2 pCi/L	Non-Smoker	~4 people	4×10^{-3}
"	Smoker	~32 people	3.2×10^{-2}
4 pCi/L	Non-Smoker	~7 people	7×10^{-3}
"	Smoker	~62 people	6.2×10^{-2}
8 pCi/L	Non-Smoker	~15 people	1.5×10^{-2}
"	Smoker	~120 people	1.2×10^{-1}
10 pCi/L	Non-Smoker	~18 people	1.8×10^{-2}
"	Smoker	~150 people	1.5×10^{-1}
20 pCi/L	Non-Smoker	~36 people	3.6×10^{-2}
"	Smoker	~260 people	2.6×10^{-1}

Source: EPA (2020b).

5.1.9.11 Common Exposure to IARC Probable and Known Carcinogens

IARC has four different categories into which it groups compounds based on evidence of carcinogenicity, based on its overall evaluation. These categories are as follows:

- The agent is *carcinogenic to humans* (Group 1)
- The agent is *probably carcinogenic to humans* (Group 2A)
- The agent is *possibly carcinogenic to humans* (Group 2B)
- The agent is *not classifiable as to its carcinogenicity to humans* (Group 3)

IARC classifies NDMA and NDEA as Group 2A compounds. IARC did not classify either NDMA or NDEA as Group 1 known human carcinogens (IARC, 2020). What needs to be recognized is that we are all exposed on a daily basis to many compounds that have been classified as known, probable, and possible carcinogens. Common exposures, including foods, medications, and certain occupations, have been evaluated and classified as carcinogenic to humans (Group 1) and probable (Group 2A) carcinogens by IARC (see Table 27 below). It is not unusual to be exposed to carcinogenic compounds.

Table 27. Selected IARC Group 2A exposures (from IARC, 2020)

IARC Group 1 Exposures — Human Carcinogens	
Alcoholic beverages Indoor emissions from household combustion of coal Diesel engine exhaust Epstein-Barr virus Estrogen therapy Estrogen-progestogen therapy Chronic infection with Hepatitis B Chronic infection with Hepatitis C Infection with Helicobacter pylori (H. pylori) Infection with HIV-1 Various Human papilloma virus types	Exposure to ionizing radiation (e.g., sun, x-rays, nuclear medicine, inside human body, rocks and soil) Outdoor air pollution Occupational exposure as a painter Consumption of processed meat Radon-222 and its decay products Tobacco smoking Second-hand tobacco smoke Smokeless tobacco Ultraviolet radiation Ultraviolet-emitting tanning devices Welding fumes Wood dust
IARC Group 2A Exposures — Probable Carcinogens	
Consuming red meat Drinking very hot beverages Emissions from frying food Working as a hairdresser or barber Night shift work Human papillomavirus type 68	Acrylamide (present in cigarette smoke and many foods) Nitrate or nitrite (ingested) under conditions that result in endogenous nitrosation Occupational in petroleum refining NDMA

Source: IARC (2020).

5.1.9.12 Carcinogenic Exposures from Smoking

Cigarette smoke has been concluded by IARC (2012) to be a known human carcinogen (Group 1), as has involuntary (or second-hand smoke), and smokeless tobacco. Cigarette smoke has been associated with numerous cancers at different sites [lung, oral cavity, oropharynx, nasopharynx, hypopharynx, esophagus, stomach, colorectum, liver, pancreas, nasal cavity and paranasal sinuses, larynx, uterine cervix, ovary, urinary bladder, kidney, ureter, and bone marrow (myeloid leukemia)]; secondhand smoke has conclusively been linked with lung cancer in humans (IARC, 2004, 2012). Smokeless tobacco has been causally linked with cancers of the oral cavity, esophagus, and pancreas (IARC 2012).

About 4,000 compounds have been identified in mainstream cigarette smoke; however, some researchers estimate there may more than 100,000 (NTP, 2016). At least 81 different known or suspected carcinogens have been identified in tobacco smoke (Hoffmann and Hoffmann, 2001; Smith et al., 2003; IARC, 2004, 2012). IARC (2012) notes:

> *There are other likely carcinogens in cigarette smoke that have not been evaluated by the IARC Monographs programme. These include, for example, PAHs with incompletely characterized occurrence levels and*

carcinogenic activities; over 500 PAHs have been identified (Rodgman and Perfetti, 2006).

Tobacco contains radioactive elements, lead-210 (^{210}Pb) and polonium-210 (^{210}Po) (Kilthau, 1996). Mainstream cigarette smoke contains 0.03–1.0 pCi polonium-210 (Table 1.14 of IARC, 2002). Kilthau (1996) estimated that the ^{210}Po intake by a typical smoker is about 0.72 pCi per pack of 20 cigarettes. Recently, Khater (2004) measured the radioactivity of ^{210}Po and ^{210}Pb in smoke and estimated that the annual effective doses for a one-pack-per-day smoker were 193 and 251 µSv, respectively. Some researchers have estimated the range of dose rates of ^{210}Po alpha particle exposure in lung epithelial tissue in smokers to be from 165 rem to 1,000 rem over a period of 25 years (Kilthau, 1996).

5.1.9.13 Summary

The point of this part of the report is not to suggest that we are at serious and immediate risk of cancer from the medications we take, the air we breathe, the water we drink, or the food we eat. Nor is the point to suggest that cancer risk estimates are meaningless because everything is risky, or even to attack regulatory agencies' methods of assessing cancer risk. Rather, the point is to emphasize that, when conducting a public health evaluation, a scientist must be careful to consider alternative causes of disease and consider other risks using the same method of analysis that was employed to estimate the risk from the alleged exposure and potential cause under consideration.

6 Summary

Overall, it is my opinion that neither NDMA nor NDEA are known human carcinogens. Further, based on my evaluation of the scientific evidence and the materials related to this case, there is no support for a causal relationship between the plaintiffs' potential exposures to valsartan-related NDMA or NDEA and any current cancer they are alleging or any future cancers they might develop. Based on the concentrations of NDMA and NDEA that were reported to be present in the valsartan at issue in this case, I have determined that the plaintiffs' exposures did not put them any increased risk above their background exposures. We all experience background exposures to endogenous and exogenous NDMA, NDEA, and other nitrosamines that represent higher exposures than the exposures the plaintiffs may have received from their valsartan medications. Additionally, all individuals experience common exposures (e.g., via food, air, drinking water, occupations, etc.) that are classified as carcinogenic exposures. Finally, regulatory guidance levels (e.g., FDA/EMA AIs) are designed to be overly conservative to ensure that they are health protective. Such levels are not the dividing line between "safe" and "unsafe" concentrations.

7 Plaintiffs' Experts' Opinions

I have reviewed the plaintiffs' experts' reports in this matter. Below are just a few comments I had on some of the opinions. These comments are in no way meant to be comprehensive.

7.1 Dr. Lagana

- On page 16 of his report, Dr. Lagana seems to imply that, based on the meta-analysis of Song et al. (2015), when the daily NDMA intake of an individual reached 120 ng, the dose-response curve for cancer became non-linear, indicating "more potency" and "more cancers." Despite Dr. Lagana's prediction that, at doses above 120 ng NDMA, there will be cancer in a population or NDMA will become more potent, there is no indication that this will actually occur. The endogenous formation of NDMA is much higher than this (see estimates by Hrudey et al., 2013).
- Dr. Lagana states in his report that "…anyone who has consumed such contaminated valsartan has assumed an unreasonable oncologic risk, having increased the risk that they will, at some point in their lives, develop cancer. From a medical and scientific perspective, anyone who consumed such products has been harmed, irrespective of whether they have suffered a clinically manifested outcome to date, because the ingestion of the contaminated valsartan has increased the risk that they will develop cancer at some point during their lives." To counter this, there is no sound scientific evidence that to prove that either NDMA or NDEA is a known human carcinogen. Further, even using risk assessment methods, which are overly health-protective, he would have seen that the potential worst-case doses of NDMA and/NDEA to which the plaintiffs might have been exposed would not have resulted in any unacceptable excess cancer risk. Further, the potential excess cancer risks that have been calculated are *theoretical*.

7.2 Dr. Panigrahy

- In his report, Dr. Panigrahy discusses the importance that inflammation plays in cancer. He cites one of his own papers several times (Fishbein et al., 2021). This paper discusses the role of failure of resolution of inflammation in carcinogenesis. He mentions numerous exposures that can "disrupt the resolution of inflammation contributing to a devastating global burden." Examples of these chemicals include alcohol and tobacco, asbestos, aflatoxins, etc.
    - In this publication, Dr. Panigrahy states, "More than 1,400 chemicals and chemical groups are known or likely carcinogens" (he lists chemicals, radiation, viruses, obesity, inflammatory bowel disease, etc.) It appears Dr. Panigrahy fails to rule out or consider potential exposure

to the compounds that are most likely relevant as potential alternative causes in the plaintiffs' cases.

- Similar to what I state in my report above, Dr. Panigrahy notes in this study that 70% to 95% of cancer cases have been traced to identified risk factors that include diet, tobacco, infections, obesity, alcohol, and others, including pollutants and radiation. Dr. Panigrahy should explain how all these large known risk factors might compare to the small theoretical risk that might be posed by possible exposure to NDMA and/or NDEA from valsartan.

- Dr. Panigrahy describes NDMA and NDEA being synergistic compounds. I note that none of the risk assessment documents for NDMA and NDEA or nitrosamines (e.g., EMA, FDA, etc.) ever mention these two compounds as acting in a synergistic manner when considering the risks of the two compounds together.

- Dr. Panigrahy relies on a study by Hidajat et al. (2019), an occupational study of rubber workers in the British industry that also evaluated NDMA exposure (along with rubber dust, rubber fumes). Aside from the fact that this type of study (i.e., occupational) evaluates inhalation exposure (rather than ingestion exposure), other shortcomings of this type of study include exposure to other chemicals, lack of appropriate control for confounders or other risk factors, and others. It should be noted that the findings of Hidajat et al. (2019) were questioned by Sorahan (2019), who stated that the findings differed from recent findings for the same cohort:

> *Hidajat et al have recently published a further report from an updated mortality study of UK rubber workers set up in the 1970s. In a statistically complex analysis based on assumed job histories, Hidajat et al. reported positive associations for a host of cancer sites and all occupational exposures that they considered (rubber dust, rubber fume, nitrosamines). Taken at face value these findings might suggest that current workers in the rubber industry are not adequately protected against cancer risks. But can the new findings be regarded as reflecting causality? Personally, I doubt that they can because they are not consistent with other recent findings from the same cohort. Let us take multiple myeloma as an example. All of the 15 HRs shown in tables 1 and 2 of ref 1 are above 1.0 (11 are above 1.5 and 5 are above 2.0), suggesting that multiple myeloma has been a major issue for most workers in the historical rubber industry. But when we go back to the SMR published recently for the same cohort we find no suggestion of an occupational problem (observed 105, SMR 1.0, 95% CI 0.82 to 1.21). There are similar conflicting findings for leukaemia, non-Hodgkin's lymphoma, prostate cancer, pancreatic cancer and liver cancer."*

I reserve the right to amend or supplement this report should new data, new allegations, or new experts and their reports become available and made part of this case.

Janice K. Britt

August 2, 2021

Janice K. Britt, Ph.D. Date
Managing Scientist

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APPENDIX A

Discussion of Animal-to-Human Extrapolation

The extrapolation of animal test results to predict the true human response is an assumption with great uncertainty.

1. The uncertainty associated with the extrapolation of animal test results may stem from either the experimental conditions of the test or the species differences in key biologic/anatomic factors.

It is often stated that that the ultimate goal in toxicology is to determine the adverse effects (toxicities) that a substance will induce in humans, and to characterize the dose ranges over which exposure to the chemical is safe or toxic. To generate this information, humans cannot be used as the first subjects on which to test the compound's toxicity; therefore, testing the chemical in a surrogate animal species provides a reasonable method—perhaps the sole method—of predicting safe or toxic doses and focusing on which adverse effects to monitor. However, there are at least two major problems with using animal models to predict human response to chemical exposure.

a. Test Conditions

The first problem is that the observed toxicities reported in any animal test may be specific to the test conditions themselves (James et al., 2000). This is because there are five components of any toxicity tests or dose-response measurement:

a. The specific species selected to be tested
b. The response (effect) selected to be measured
c. The exposure interval over which the chemical is administered to the test species
d. The observation period over which the selected response is measured
e. The range of doses to be tested.

A change in any one of these components of every toxicity test can alter the response observed and the response rate (i.e., may determine the very outcome of the test performed). For example, the following table demonstrates that two closely related rodent species may provide completely different responses, depending on the concentration of the chemical to which the species was exposed.

Chloroform inhalation studies

Species	Toxicity of Interest	Duration of Exposure	Exposure/Dose (ppm)
Mouse	No effect — liver	6 h/day for 7 days	3
Mouse	Mild liver damage	6 h/day for 7 days	10
Mouse	Severe liver damage	6 h/day for 7 days	100

Species	Toxicity of Interest	Duration of Exposure	Exposure/Dose (ppm)
Mouse	No effect — kidneys	6 h/day for 7 days	100
Mouse	Mild kidney injury	6 h/day for 7 days	300
Mouse	No effect — respiratory	6 h/day for 7 days	300
Rat	No effect — respiratory	6 h/day for 7 days	3
Rat	Nasal injury	6 h/day for 7 days	10
Rat	No effect — kidneys	6 h/day for 7 days	10
Rat	Mild kidney injury	6 h/day for 7 days	30
Rat	No effect — liver	6 h/day for 7 days	100
Rat	Mild liver damage	6 h/day for 7 days	300

Reproduced from James et al. (2000), as adapted from ATSDR (1996), Toxicant Profile for Chloroform.

As this table shows, liver toxicity is the most sensitive endpoint in the mouse, but in the rat, the nasal or upper respiratory tract is the most sensitive organ. Probably due to chance alone, both species appear to have the same no-observed-effect level (NOEL) for the most sensitive endpoint that the chemical induces, and this NOEL would be 3 ppm for both species. However, at a 10-fold higher concentration, the only effect seen in mice is one of mild liver toxicity, whereas at 30 ppm, both nasal injury and kidney toxicity would be seen in the rat. Likewise, if respiratory-tract injury and kidney function were the only two endpoints being monitored when testing chloroform toxicity in these two closely related rodent species, and if the chloroform test concentrations were limited to those between 1 ppm and 100 ppm, then the mouse might erroneously be considered to be a species that was completely resistant to any chloroform-induced toxicity at these concentrations. Similarly, predicting the NOEL for kidney toxicity based on testing performed in the mouse would not prevent kidney toxicity from occurring in the rat when tested at the NOEL concentration for the mouse. Thus, this table provides several examples of how changing one of the five basic components of a toxicity experiment may change the outcome observed in a particular species.

b. Species Selection

The second major problem, and one that contributes to the problem of test conditions resulting in responses specific to the conditions of the test, is the problem of species selection. While we generally rely exclusively on animal toxicity tests using rodent species, because they are more cost-effective to raise and house before and during the experiment, there are numerous key differences between humans and rodent species, including:

1. Basal metabolic rates
2. Anatomy and organ structure
3. Physiology and cellular biochemistry
4. Basic pharmacokinetic and pharmacodynamic factors may vary across species
5. The metabolism, bioactivation, and detoxification of a chemical and its toxic or reactive metabolites may vary quantitatively and qualitatively across species.

For example, humans have gallbladders, but rats do not. Zymbal gland tumors and forestomach tumors are observed frequently in rodent studies, but humans lack these anatomical structures. Thus, the induction of animal tumors by chemicals at only these anatomical sites is likely to represent a finding of little or no relevance to humans. For example, chemicals that induce forestomach tumors in rodents, but the human relevance of this observation is considered to be lacking, include the food additive BHA (butylated hydroxyanisole), propionic acid, and ethyl acrylate (Faustman and Omenn, 2001, see Table 4; see Proctor et al., 2007, Table 3, for the authors' recommended criteria for assessing the human relevance of forestomach tumors). Similarly, the Fischer 344 rat, a rat strain frequently used in animal cancer bioassays, has a high background incidence of Leydig cell tumors, and a number of chemicals have been shown to induce statistically significant increases in this tumor type. However, the consensus scientific opinion regarding this finding is that it essentially has no human relevance (Steinbach et al., 2015; Maronpot et al., 2016). Similarly, key physiologic or biochemical species differences are seen for a number of chemicals (e.g., gasoline and d-limonene) that have been shown to produce kidney tumors in male rats but not in female rats or male and female mice. The mechanistic explanation for this specific sex and species disparity has been shown to stem from the fact that male rats have relatively large amounts of a unique protein (alpha$_{2\mu}$-globulin) that is adversely affected by these chemicals (or their metabolites), leading to recurrent renal cell necrosis, regenerative hyperplasia, and ultimately neoplasia (Faustman and Omenn, 2001). In contrast, the nonresponsive sex or species has no or only insignificant amounts of this protein, and exposure to these chemicals does not induce the same pathology and tumor that is observed in the male rat. Given the limited and unique biochemical basis for the observed renal cancers in rats, scientists and regulatory agencies have concluded that chemicals that induce renal tumors via this mechanism do not pose a relevant or significant human risk (Dietrich and Swenberg, 1991; Swenberg, 1991; Swenberg, et al., 1992; Faustman and Omenn, 1996; Omenn, 1995; Williams and Whysner, 1996; Faustman and Omenn, 2001).

Ethyl benzene, a major component of gasoline and a chemical to which we are all exposed on a daily basis, has been shown to induce renal tumors in Fischer-344 rats via a secondary mechanism that involves the exacerbation of chronic progressive nephropathy (CPN), a spontaneous and age-related disease seen in rodents (Hard, 2002). There is no counterpart to this disease in humans, and so, this particular type of animal bioassay result should not be considered a finding that is relevant to human risk considerations (Hard, 2002; Hard et al., 2007).

Saccharin presents another example where the biological differences in rodents produces a high-dose tumorigenic response that is not relevant to the lower doses to which humans are exposed. At high doses, the formation of crystals in the urine of male rats induces recurrent cytotoxicity and cellular hyperplasia, an epigenetic mechanism that has a threshold well above those doses occurring in the human population (Williams and Whysner, 1996; Faustman and Omenn, 2001). Additionally, nonhuman primates exposed chronically to doses 5- to 10-fold higher than the human ADI for saccharin experienced no crystal formation, no cell proliferation, and no tumor formation within the urinary tract (Takayama et al., 1998). Given this mechanism, and the lack of similar outcomes in humans and nonhuman primates, this chemical is considered to be a rodent carcinogen that is of no relevance to human risk (Morgan and Wong, 1985; Ellwein and Cohen, 1990; Elcock and Morgan, 1993; Whysner and Williams, 1996; Takayama et al. 1998; IARC, 1999). Other chemicals that induce bladder tumors in rats via this species-specific mechanism include melamine and nitrilotriacetic acid (Faustman and Omenn, 2001).

Atrazine is an herbicide that has been found to induce mammary tumors in female Sprague-Dawley rats (responsive rat strain) but not female Fischer-344 rats (nonresponsive rat strain). In the responsive strain, atrazine affects the hypothalamus and inhibits the luteinizing hormone surge that occurs during the estrous cycle of the responsive strain, which in turn produces a persistent secretion of estrogen and prolactin. These changes are not induced by atrazine in the nonresponsive rat strain, nor are they seen in CD-1 mice, a species that also does not develop mammary tumors. Furthermore, even if atrazine did affect the hypothalamus of humans, a hypoestrogenic response would be expected. Thus, it can be concluded that the atrazine-induced mammary tumors, an effect not seen in the Fischer-344 rats or CD-1 mouse, is not a relevant outcome for humans (Cohen et al., 2004).

Trichloroethylene (TCE) is a chemical that underscores the problems associated with species differences in the metabolism of chemicals. Although the mouse and the rat metabolize TCE to the same metabolites (qualitative agreement), there are significant species differences in the rate of oxidative metabolism, and in the pharmacokinetics and pharmacodynamics of the metabolites generated, that seem to explain the species differences observed in the tumorigenic responses after chronic, high exposure to this chemical. In the mouse, but not the rat, inhalation exposure to TCE induces lung tumors. After studying this phenomenon extensively, Green (2000) provided a well-described mechanism of action showing that key biochemical and cellular responses were mouse > rat >> humans. Given that the rat is the nonresponsive species at high exposure levels, one would not expect TCE to induce lung cancer, even in TCE-exposed workers. This conclusion has been borne out in the epidemiology studies (Scott and Chiu, 2006).

A number of drugs (e.g. phenobarbital) and chemicals capable of inducing drug-metabolizing enzymes in the liver (e.g., cytochrome P-450 and glucuronyltransferase) have been shown in animal cancer bioassays to induce thyroid tumors in rodent test species such as the mouse and the rat (Cohen et al., 2004; Capen, 2001). This increase in liver metabolism lowers the animal's serum thyroid hormone levels. This decrease triggers a normal homeostatic control mechanism that stimulates the pituitary to release more TSH (thyroid-stimulating hormone) into the bloodstream, which then stimulates the thyroid to produce and release more thyroid hormones. Because these changes are chronic, the

constant TSH stimulus of the thyroid first induces hyperplasia in the follicular cells of the thyroid, and ultimately, thyroid tumors. In fact, there are a number of important drugs that induce thyroid tumors in rats secondary to a disruption of serum thyroid hormone levels; these include drugs from important drug classes such as the antibiotic, calcium channel blocker, antidepressant, hypolipidemic, diuretic, and antiviral drugs (Capen, 2001). However, human liver enzyme induction does not produce this same cascade of events, and so, humans do not develop thyroid tumors as a result of exposure to chemicals that induce thyroid tumors in rodents via the liver induction mechanism or other secondary decreases in serum thyroid hormone levels (Cohen et al., 2004; Capen, 2001). In fact, humans, in general, are relatively resistant to the development of thyroid tumors, even following a chronic elevation in plasma TSH levels, such as that seen in cases of goiter. In fact, there is no evidence of an increase in thyroid cancer in geographic areas where goiter is endemic. In short, there are a number of important chemicals that induce thyroid cancer in rodents, for which the corresponding human risk is believed to be zero, especially at the doses to which humans are exposed to these chemicals (Capen, 2001).

The plasticizer di-(2-ethylhexyl)-phthalate (DEHP) induces rodent liver tumors via a nongenotoxic, receptor-mediated mechanism that involves the PPARα-receptor. Studies have shown that it has a nonlinear dose-response curve, suggesting the existence of a threshold below which no tumors are observed (Doull et al., 1999). Given this finding, the lower human expression of the PPARα receptor, and the fact that liver tumor induction via the PPARα receptor represents a well-understood mechanism in rodents that is generally believed to be of limited or no human relevance, Doull et al. (1999) concluded that this response in rodents to DEHP was not relevant to the human risk assessment for this particular compound.

Given the many differences in anatomy, physiology, biochemistry, and gene expression that exist between rodents and humans, concern has also been raised for those rodent tumorigenic responses induced by a nongenotoxic chemical, or via a nongenotoxic mechanism for a specific chemical, when the tumorigenic response occurs in a rodent organ that has a very high incidence of spontaneous neoplasms relative to that of humans. Examples include, but are not limited to, lung tumors in strain A mice, liver tumors in mice (especially the B6C3F1 strain), and the occurrence of Leydig cell tumors in rodents (ECETOC, 1982; Grisham, 1996; Cook et al., 1999). For example, the reported human incidence of Leydig cell tumors (LCTs) in humans is some 132,500 to 1,920,000 times lower than the spontaneous incidence seen in the Fischer-344 and CD strains of rat. Lactose, a natural sugar and component of milk and all dairy products, has been shown to induce LCTs in Wistar rats; however, despite the ubiquitous exposure of humans to lactose, there is no evidence that it is associated with an increase in LCT incidence in man (Cook et al., 1999). Similarly, alcohol and nicotine are two chemicals to which human exposure is common, and yet, no epidemiologic evidence indicates that either chemical induces LCTs in humans (Cook et al., 1999).

To summarize, there are a number of anatomical, biochemical, physiologic, and genetic reasons why any species extrapolation for a disease as biologically complex as cancer is fraught with difficulty and uncertainty (Ashby et al., 1994; Ellwein and Cohen, 1990; Alison et al., 1994; IARC, 1995; Omenn, 1995; Saccharin Expert Panel, 1985; IARC, 1999;

Williams and Whysner, 1996; Grisham, 1996; Cook et al. 1999; Boivin-Angele et al., 2000; Capen, 2001; Cohen et al., 2004; Perel et al., 2007).

2. Limitations and Errors Caused by the Use of the Maximum Tolerated Dose in Chronic Animal Cancer Bioassays

One frequently cited problem regarding the extrapolation of rodent bioassay results to humans is the almost exclusive use of extremely high, chronic dosages of the test chemical. The standard protocol for performing chronic animal cancer bioassays includes testing the chemical at its maximum tolerated dose (MTD). Theoretically, the MTD is the highest dose at which the normal bodily functions of the animal are not *significantly* interrupted, and the intended purpose of the MTD is to ensure that the carcinogenic potential is not missed on the basis of the dose selected. In other words, the goal of the testing protocol is to ensure that negative responses cannot be criticized as possibly resulting from testing of an inadequate dose. Unfortunately, because the animal test doses are so high, and humans are frequently exposed to levels of the chemical that are orders of magnitude lower, these high-dose animal findings may easily have no, or at best, limited relevance to the lower exposure levels experienced by human populations (Ames et al., 1987; Cohen and Ellwein, 1992; Gold, 1993; Goodman, 1994; Pitot and Dragan, 1996; Squire, 1984). This is because dosing at the MTD may create biochemical and cellular responses that simply do not occur at lower, environmental exposures to the chemical (Squire, 1984; Ames, 1989, Ames and Gold, 1991; Ames et al., 1987; Butterworth et al., 1995a,b; Golden et al., 1997; Doull et al., 1999). For example, the MTD may be sufficient to cause cell toxicity and death in certain organs, which stimulates chronic repair, cell growth, and replication. Increased cell replication may act as either a spurious initiating or a promoting factor in carcinogenesis by introducing an error in DNA replication, or by providing a stimulus for the preferential growth of cells already initiated. Lower doses that do not cause cell death would not produce errors in DNA replication, promote the fixation of mutations, or stimulate the growth of cells already altered. Therefore, the lower doses may carry no risk of cancer at all (Ames, 1989; Cunningham and Matthews, 1995; Cunningham et al., 1989, 1991, 1994a,b; Shaw and Jones, 1994; Pitot and Dragan, 1996; Yoshikawa, 1996).

Consistent with the potential for the MTD to induce physiological and biochemical conditions within the animal that are unique to the higher doses being tested is the work of Meijers et al. (1997). They studied a small subset of 35 carcinogenic chemicals listed in the IARC Monographs. The seven chemicals that showed no or unclear carcinogenic effects in humans were more likely to have had toxic side-effects in the bioassay test, indicating that the test conditions were above the MTD. These chemicals also more often showed effects at multiple sites than did those chemicals for which clear human evidence of a carcinogenic effect was found; and these chemicals likewise tended to have lower cancer potency estimates when the animal data were extrapolated. The authors cautioned that observing carcinogenic effects in multiple organs in animals may be a manifestation of high-dose toxicity that produces a finding of limited predictive value in humans (Meijers et al., 1997).

In short, in the past two decades, it has become increasingly apparent that changes induced by high-dose toxicity may result in positive carcinogenic responses via mechanisms that are not relevant to lower doses, particularly those commonly associated with human exposures (some examples include peroxisomal proliferation, reactive oxygen species generated during chronic inflammation, recurrent cytotoxicity as a stimulation for mitosis or as a factor producing the hypomethylation of oncogenes), and this issue has been recognized by regulators and research scientists alike (Squire, 1984; EPA, 1986; Ames et al., 1987; EPA, 1987, 1996; Gehring, 1989; Ames and Gold, 1990; Swenberg et al., 1995; Slikker et al., 2004a,b). Concerns have been raised that many chronic animal bioassays may derive results that are limited to cellular conditions associated only with high doses. Gold et al. (1998) showed that ~50% of all chemicals tested in the chronic animal bioassay could be classified as an animal carcinogen. This percentile was essentially the same whether the chemical being tested was synthetic or natural, was useful industrially, was a medication, or was found only in food items (see the following table adapted from Ames and Gold, 2000). Thus, the expected number of animal bioassays that will produce results relevant to only the species tested, and/or the high doses tested, is large indeed. Conversely, it is therefore common for an animal bioassay to produce positive results for which the scientific community believes the findings are of limited or no relevance to humans exposed to much lower levels of the chemical.

Proportion of chemicals evaluated as carcinogenic

	Proportion	Percentage
Chemicals tested in both rats and mice	350/590	59%
Naturally occurring chemicals	79/139	57%
Synthetic chemicals	271/451	60%
Chemicals tested in rats and/or mice		
Chemicals in the carcinogenic potency database	702/1348	52%
Natural pesticide	37/71	52%
Mold toxins	14/23	61%
Chemicals in roasted coffee	21/31	71%
Physician's Desk Reference (PDR)		
Drugs with reported cancer tests	117/241	49%
FDA database of drug submissions	125/282	44%

Source: Ames and Gold (2000).

The conclusion that it is highly likely that MTD exposures to animals can create unique toxicological responses in test animals is easily illustrated by the results of animal cancer bioassays themselves. For example, one analysis has shown that44% of the animal cancer bioassays reported no significant cancer incidence in the animals when the dose was reduced to just one-half of the MTD (Gold, 1993). Therefore, Gold has shown that, while a positive carcinogenic response would be expected for one-half of all the chemicals not

yet tested, almost half of these chemicals will produce a positive only at the MTD, and lower doses will not be carcinogenic.

Despite these and other obvious shortcomings associated with the current animal cancer bioassay protocol, the regulatory-based carcinogenicity classification scheme currently used by the EPA generally accepts any positive animal result. That is, a chemical may be referred to as a "probable human carcinogen" whenever there is "sufficient evidence from animal studies," even though the carcinogenic response may be limited to doses at or near the MTD or may be observed in a uniquely sensitive rodent species.

3. Empirical Evidence Demonstrates that Target Organ Extrapolations Can Be of Limited Reliability

The potential reliability of making target-organ extrapolations between the animal species tested and humans can be evaluated only by examining the results available for those chemicals classified as known human carcinogens. Analyzing the 27 known human carcinogens, as classified by IARC, only 63% of the compounds evaluated had the correct target organ in *some* species of animal tested. However, this percentage overstates the actual predictive power of animal tests, because many of the chemicals for which at least one species correlated correctly were chemicals for which there were also other animal strains or species that did not correlate correctly by tissue affected. For 10 of the 27 compounds, no animal species tested could be extrapolated correctly as to the target organ affected in humans. In addition, when all positive animal results for these 27 known human carcinogens are examined collectively (i.e., 147 positive results from the 27 compounds studied), the overall percentage of animal tests that correctly indicated the correct target organ in humans was only 31%.

In fact, animal carcinogenicity studies do not even reliably predict the tissue that will be afflicted with cancer in two closely related rodent species (e.g., mouse to rat). Haseman and Lockhart (1993) examined 379 long-term National Cancer Institute/National Toxicology Program studies in rats and mice for possible associations for site-specific carcinogenic effects. The target organs used in the evaluation were the 13 most frequent sites of cancer observed in chronic animal bioassays. The results of this study are summarized in the following table.

Poor correlation in organ sites of cancer in rodent tests

Site of Cancer	(Rats v. Mice)	Percent	(Mice v. Rats)	Percent
Liver	25/33	75	25/78	32
Lung	2/7	29	2/18	11
Hematopoietic System	3/14	21	3/11	27
Kidney (Tubular Cells)	3/21	14	3/4	75
Mammary Gland	4/18	22	4/7	57
Forestomach	8/14	57	8/15	53
Thyroid Gland	7/16	44	7/9	78
Zymbal Gland	2/12	17	2/2	100
Urinary Bladder	2/12	17	2/3	67
Skin	3/11	27	3/3	100
Clitoral/Preputial Gland	0/7	-	0/3	-
Circulatory System	2/4	50	2/10	20
Adrenal Medulla	0/4	-	0/4	-
Total	**61/173**	**35%**	**61/167**	**37**

Adapted from Haseman and Lockhart (1993).

This table demonstrates a clear and unequivocal lack of agreement in the organ site affected by chemically induced cancer when comparing two phylogenetically similar species such as mice and rats (Haseman and Lockhart, 1993). Across these two closely related species, the predictability of test results was found to be, on average, much less than 50%, causing Haseman and Lockhart (1993) to conclude:

> *Our evaluation revealed a number of target sites showing significant associations in chemically related carcinogenic responses between species. However, such agreement was far from complete, and the overall probability that a chemical carcinogenic at a particular site in rats will be carcinogenic at the same site in mice (and vice versa) is approximately 36%.* (Haseman and Lockhart, 1993; emphasis added)

Thus, even between two genetically similar rodent species such as the rat and mouse, the tissue-predictive value of a positive carcinogenic effect in one species was accurate only 35% and 37% of the time, respectively.

4. Empirical evidence demonstrates that species extrapolations of carcinogenic outcome have poor correspondence, even among closely related rodent species

Several studies have empirically examined the predictability of rodent cancer bioassays and found poor reliability in species extrapolations for the chemical's carcinogenic potential in a second rodent species. Haseman and Huff analyzed 327 long-term animal cancer bioassay studies reported by the National Toxicology Program and selected 266 chemicals for which there was sufficient information on the responses of both sexes of rats and mice. Haseman and Huff (see Haseman and Huff, 1987, and Huff and Haseman, 1991) have suggested that there was good overall agreement between species (a concordance of 74%) when all test results they evaluated were considered. However, closer examination of their data reveals that this level of agreement between the two closely related species, rat and mouse, was due largely to the fact that 49% of the chemicals tested and evaluated were non-carcinogens (James and Saranko, 2000). If one measures the reliability of species extrapolation for those chemicals thought to be carcinogenic (i.e., the positive predictive value), the agreement between these two species is actually far lower. In fact, the predictability of test results has always been less than 50% (James and Saranko, 2000).

The summary tables shown on the next page are taken from the results reported in Haseman and Huff (1987) and Huff and Haseman (1991). To determine the positive correspondence between these two rodent species, the number of positive (+) results between species is compared to the total number of "+/+, +/–, -/+" results for each sex of these two rodent species. When this is done, one derives the results shown.

Summary table for Haseman and Huff (1987): Correlations in tumor response in NCI/NTP carcinogenicity studies

Comparison	+/+	++, +/-, and -/+	Concordance
Male rats to male mice	38+1+5+1=45	38+1+10+5+5+16+1+4+1 +23+13+7=124	45/124= 36%
Male rats to female mice	38+10+5+4=57	38+1+10+5+5+16+1+4+2 +23+13+6=124	57/124= 46%
Female rats to male mice	38+1+5+1=45	38+1+10+5+5+16+1+1+2 +23+3+7=112	45/112= 40%
Female rats to female mice	38+10+5+2=55	38+1+10+5+5+16+4+1+2 +23+3+6=114	55/114= 48%

Adapted from Haseman and Huff (1987), from data presented in their Table 1.

Summary table for Huff and Haseman (1991): Correlations in tumor response in NCI/NTP carcinogenicity studies

Comparison	+/+	++, +/-, and -/+	Concordance
Male rats to male mice	43+1+7+2=53	43+1+11+7+6+19+2+7+ 2+23+17+9=147	53/147= 36%
Male rats to female mice	43+11+7+7=68	43+1+11+7+6+19+2+7+ 3+23+17+8=147	68/147= 46%
Female rats to male mice	43+1+6+2=52	43+1+11+7+6+19+2+2+ 3+23+4+9=130	52/130= 40%
Female rats to female mice	43+11+6+3=63	43+1+11+7+6+19+7+2+ 3+23+4+8=134	63/134= 47%

Adapted from Huff and Haseman (1991), from data presented in their Table 3.

As these results demonstrate, extrapolating positive carcinogenic potential between two phylogenetically similar species such as rats and mice yields a correct answer less than 50% of the time. In addition, as the number of animal bioassays being evaluated was increased between 1987 and 1991, the reliability of this extrapolation did not improve. Thus, the empirical measurement of the limited reliability of using positive bioassay results in one species to accurately predict the carcinogenic potential of the same chemical in a second closely related species, such as that between rats and mice, is not likely to change substantially with even larger studies of this issue. Because this species extrapolation cannot be performed reliably in two genetically similar species such as mice and rats, this suggests that one should expect a similarly low, if not an even lower, level of reliability when attempting the same extrapolation between genetically more diverse species such as rodents and humans.

Another analysis of the potential usefulness of animal bioassay data for identifying human carcinogens was reported decades ago by Ennever et al. (1987). This study analyzed the sensitivity (the ability to detect human carcinogens) and specificity (the ability to identify chemicals that are not carcinogenic in humans) of animal bioassays by comparing the results of animal testing to the available epidemiologic evidence. Using evaluations by the International IARC, the authors identified 29 chemicals with evidence of noncarcinogenicity and 17 chemicals for which the evidence of human carcinogenicity was considered sufficient. Of the ten human carcinogens that had been tested in both sexes of a single species, positive animal tests were reported for all ten compounds. This suggests that animal testing is quite sensitive (100%) in identifying *known* human carcinogens. However, for the 20 chemicals considered to be noncarcinogenic in humans, 19 tested positive in at least one animal test of carcinogenicity. This indicated that animal cancer bioassays lack specificity, and that a large percentage of false positives (in this analysis, 95%) are apparently generated by animal testing.

The results of the studies such as those by Ennever et al. (1987) perhaps most clearly illustrate why animal cancer testing, though useful for regulatory purposes, may contribute little to the scientific process of determining causation. Animal testing appears to meet the needs of the regulatory agencies because of its excellent sensitivity. The apparent low false negative rate means that it is generally unlikely that animal testing will fail to identify a compound that will later be shown to be a human carcinogen. (Note, however, that there are three rather significant exceptions: arsenic, benzene initially, and cigarette smoking.) As several of the aforementioned analyses have shown, though, a large percentage of compounds thought to be carcinogenic in animals are not likely to be carcinogenic in humans, at least at the much lower environmental doses to which humans are typically exposed.

While considering this issue, it should be noted that a government policy publication entitled, the *Regulatory Program of the United States Government* (1991, NTIS PB90-238585) reached a similar conclusion:

> *Animal testing suffers serious limitations, however, arising from certain critical assumptions. Despite its routine application, there is no accepted scientific basis for the assumption that results can be meaningfully*

extrapolated from test animals to humans. Some scientists believe that animal data should not be used in assessing human health risks.

And,

Of course, this ratio of false positives to false negatives reflects highly conservative "upper-bound" assumptions concerning sensitivity and selectivity. Given the high degree of similarity between rats and mice and the limited resemblance between rodents and humans, the sensitivity of rodent bioassays with respect to human carcinogenicity is probably much lower than 70 percent. Furthermore, other research indicates that selectivity may be as low as 5 percent. Adjusting only for this lower selectivity suggests that false positives are almost 30 times more common than false negatives. This raises serious questions concerning the practical utility of the current approach to animal bioassays for the purpose of quantitative risk assessment.

5. Empirical evidence indicates that rodent bioassays do not yield highly reproducible results.

Gottmann et al. (2001) attempted to determine how reproducible animal cancer bioassay might be by comparing the results of tests generated in the National Toxicology Program to that of chemicals evaluated in other protocols, as reported in the Carcinogenic Potency Database (CPDB). This comparison allows for determination of the percentage of replicate responses seen when a chemical is tested again. The authors identified 121 chemicals that had been tested and provided results in both databases. These authors reported finding that "*an unexpectedly low proportion of these 121 compounds were classified concordantly as carcinogens or noncarcinogens*." Of these 121 comparisons, only 69 (57%) had the concordant conclusions (i.e., the chemical had the same classification in the replicate test). Of these 39/69 chemicals (again 57%) were classified consistently as positive, and 30/69 were consistently classified as negative. Thus, 43% of the time (52 chemicals) have discordant classifications between the two experiments. The mouse test results proved to be the less consistent of the two species, with only 49% of the 70 mouse experiments that provided repeatable results. Of 71 rat experiments, the results were in agreement only 62% of the time. When evaluated by sex and species, test agreement was 46% for male mice, 36% for female mice, 55% for male rats and 69% for female rats. Because the test comparisons might involve strain differences within a species, the results were also broken down into tests using the same rat (Fischer-344) and mouse (B6C3F1) strains. Interestingly, the test agreement was now slightly lower; in general, it was 57% for male rats, 64% for female rats, 39% for male mice, and 33% for female mice. Thus, the poor reproducibility of carcinogenic responses seen in the first analysis was not caused by strain differences and variations in the strain being tested for a particular chemical. While the authors did note the possibility that the poor agreement between test results may have been increased by different laboratories using different protocols, until more information becomes available to examine more tests using the same protocol, they concluded:

> *These results indicate that rodent carcinogenicity assays are much less reproducible than previously expected, an effect that should be considered in the development of structure activity relationship models and the risk assessment process.* (Gottmann et al. (2001)

6. An analysis of noncancer responses indicates that animal test species extrapolations are also poor predictors of human response.

Olson et al. (2000) summarizes results of a multinational pharmaceutical survey that attempted to analyze the agreement between toxicity tests performed in animal species and the results of human toxicity observations identified in the subsequent clinical trials. This study was limited to those drug-induced toxicities that were severe enough to either terminate the development of the drug or to limit the dosage used, restrict drug use to required monitoring, or restrict the target population. In this manner, the confusing complication of addressing the myriad of minor side-effects typically associated with almost all drugs was avoided. Still, 221 examples of human toxicity for 150 different drugs were ultimately available for analysis using these selection criteria. The toxicity correlations between the human response and the animal test species were loosely defined as any effect that involved the same target organ, a choice that essentially inflates the incidence of the species extrapolation agreement that was eventually reported.

The overall true positive concordance was stated to be 70% when species were compared. When broken down by the species tested, the nonrodent species were in target-organ agreement 63% of the time (primarily the dog), while rodent species were reliable only 43% of the time (primarily the rat). Furthermore, only 36% of the time was the human toxicity observed with two species (a rodent and nonrodent). The total animal agreement was highest among Phase 1 clinical trials (75%), but much lower on Phase 2 (58%) and Phase 3 (52%) clinical trials. Analyzing the false negative animal findings, the authors found that, when an adverse human response was not predicted, some 91% of the rodent and 90% of the nonrodent toxicology tests were judged to still have been performed at doses approximating the MTD. Therefore, insufficient dosing was not an explanation for the false negative data. Similarly, the animal metabolism profile was considered to correlate with that of man in 86% of the false negative responses that were analyzed. Therefore, differences in metabolism are not a likely explanation for the false positive rate. In fact, 89% of the time, the animal and human metabolism correlated when considering both concordant and nonconcordant test results. Thus, species differences in the metabolism of the chemical are not likely to be the basis for discordant animal extrapolations.

To summarize, rodents are the mainstay of toxicity studies performed on industrially and environmentally important chemicals. Rodent species produced poor predictions of the human toxicity, even though concordance was measured by an effect in the same target organ, and not by inducing the same toxicity or adverse endpoint.

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BRITT

EXHIBIT A

ToxStrategies
Innovative Solutions
Sound Science

Janice K. Britt, Ph.D.

MANAGING SCIENTIST

CONTACT INFORMATION

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PROFESSIONAL PROFILE

Dr. Janice Britt is a Managing Scientist with ToxStrategies and is based in Tallahassee, Florida. She has more than 20 years of experience in toxicology and has worked in the areas of human and animal toxicology, chemical exposure assessment, dose-response analysis, and risk assessment. Dr. Britt also has extensive experience in the areas of systematic review, causation analysis, and Evidence-Based Toxicology. She recently published a 10¬year retrospective on the use of evidence-based methods in assessing causation in toxicology. She has critically evaluated the toxicity of numerous environmental- and occupational-related chemicals, pharmaceutical compounds, over-the-counter medications, dietary supplements, food and beverage products, food additives, herbal products, consumer products, and medical devices. She has evaluated exposures involving hazardous waste sites, chemical releases, environmental exposures, exposures in the home and workplace, as well as agriculture-related exposures. Specific compounds that Dr. Britt has worked with include benzene, toluene, chlorinated solvents (e.g., trichloroethylene, tetrachloroethylene, and vinyl chloride), talc, formaldehyde, chlorine, PFAS compounds (e.g., PFOA and PFOS), pesticides (e.g., acephate, atrazine, carbaryl, chlorpyrifos, cyfluthrin, 2,4-D, DDT, diazinon, dicamba, dichlorvos, diquat, heptachlor, glyphosate, limonene, malathion, methoprene, paraquat, parathion, permethrin, and simazine), paints, petroleum products, dyes, N-nitrosodimethylamine (NDMA), acrylamide, heavy metals (e.g., arsenic, lead, manganese, and mercury), polychlorinated biphenyls (PCBs), carbon disulfide, asbestos, silica, talc, sunscreens, carpet emissions, caprolactam, phosphogypsum, ammonia, fire suppressants, hydraulic fracturing-related compounds, and carbon monoxide, as well as a variety of pharmaceutical agents (e.g., acetaminophen, narcotics), herbal products, and products contained in cosmetics and foods (e.g., diacetyl, food colorants, sweeteners). Dr. Britt has conducted toxicity assessments to evaluate the hazards associated with different occupations and exposures, including painting, welding, printing work, photo processing work, mining, sandblasting, petroleum refinery work, and hydraulic fracturing. She has also performed site-specific risk assessments, developed toxicological profiles for various chemicals, evaluated various regulatory toxicity criteria, and developed safe levels of exposures for chemicals.

Dr. Britt is a member of the Society of Toxicology, the Society for Risk Analysis, the American Conference of Governmental Industrial Hygienists (ACGIH), and EUROTOX. In addition, she is a European Registered Toxicologist (ERT) and a fellow of the Royal Society of Biology (FSRB). She is currently serving as a member of USEPA's Human Studies Review Board, which is a federal advisory committee that provides advice and recommendations on issues of human subject research.

Previously, Dr. Britt worked as the toxicologist for the Florida Department of Agriculture and Consumer Services, where she reviewed toxicity data and made regulatory decisions regarding the registration of pesticides for the State. While at the Department, she served as a toxicologist on the Florida Pesticide Registration Evaluation Committee, which is responsible for conducting scientific and technical reviews of pesticide product registrations for the State of Florida. She played an active role in developing a regulatory procedure for ranking pesticides according to their chronic toxicity and leaching potential, an approach that was published in the peer-reviewed literature.

EDUCATION AND DEGREES EARNED

Ph.D., Toxicology, Texas A&M College of Veterinary Medicine and Biomedical Sciences

B.S., Zoology, Texas A&M University

PROFESSIONAL ASSOCIATIONS

USEPA Human Studies Review Board

PROFESSIONAL ASSOCIATIONS

Society of Toxicology (Risk Assessment Specialty Section; Southeastern Regional Chapter)

European Registered Toxicologist (ERT)

Society for Risk Analysis

American Conference of Governmental Industrial Hygienists

Fellow, Royal Society of Biology

EUROTOX

JOURNAL PEER REVIEWER

Regulatory Toxicology and Pharmacology

Food and Chemical Toxicology

Human and Experimental Toxicology

PROFESSIONAL EXPERIENCE

Chemical-Specific Toxicity Assessments

Evaluation of Leukemia and Painting: Completed an evidence-based review of the occupation of painting as it relates to leukemia, particularly acute myelogenous leukemia (AML). As part of this review, evaluated the background incidence and risk factors for AML.

Benzene and Hematopoietic Cancer Evaluation: Conducted a comprehensive review of the literature related to benzene and hematopoietic cancers, including various types of leukemia, non-Hodgkin's lymphoma, and multiple myeloma.

Critical Review of Solvent Encephalopathy: Critically reviewed the published literature pertaining to the issues surrounding "painters' syndrome," also known as "chronic toxic encephalopathy" or "solvent encephalopathy." Reviewed the literature for effects on neurobehavioral test scores, control for confounders, and reversibility of effects. Drafted a primer summarizing the findings.

Leukemia and Occupation as a Seaman: Considered the epidemiological literature concerning individuals working as seamen, seafarers, or marine engineers, to assess the potential risk of leukemia.

Review of the Toxicity and Risks of Hydraulic Fracturing Compounds: Conducted a comprehensive review of the toxicity of multiple compounds used in hydraulic fracturing (e.g., hydrochloric acid, acetic acid, isopropanol, magnesium oxide, citrate, guar gum) and the assessment of risk associated with drinking water.

Review of the Toxicity of Formaldehyde: Conducted an evidence-based evaluation of the irritancy effects of formaldehyde from emissions from housing units. As part of this project, conducted a comprehensive review of the pharmacokinetics of formaldehyde and exposures of humans to background levels of formaldehyde.

Toxicity of Black Liquor: Reviewed the toxicity and potential effects of black liquor from the pulp and paper industry.

Evaluation of Perchlorate Exposure and Toxicity: Conducted a thorough review of animal and epidemiologic studies of perchlorate toxicity. Created a toxicological profile for client.

Evaluation of Toxicity of Coke Plant Emissions: Reviewed air-monitoring data for emissions near a coke plant to determine whether residents near the plant were at excess risk for health effects.

Diesel Exhaust and Kidney Cancer: Researched the carcinogenicity of diesel exhaust with regard to kidney cancer.

Toxicological Evaluation of PFOA: Evaluated the human health risks of exposure to perfluorooctanoic acid (PFOA) based on a comprehensive review of laboratory animal, epidemiologic, community, and metabolic studies. Evaluated potential health effects associated with measured levels in community drinking water, as well as against serum PFOA levels measured in a human population.

Review of Toxicity of Metalworking Fluids: Evaluation of the potential health effects associated with exposure to metalworking fluids.

Autism and Hazardous Wastes: Reviewed health claims from exposures to postnatal exposure to hazardous wastes in soils (including mercury, lead, and PCBs).

Asthma and exposure to VOCs: Reviewed the literature related to low-level environmental exposure to various VOCs, to evaluate whether a causal association with asthma was present in humans.

Review of Toxicity of Glyphosate: Conducted a review of the reproductive and developmental toxicity of glyphosate in animals and humans, as well as a review of its regulatory status.

Solvent Toxicity Review: Conducted several thorough reviews and evaluations of the literature of the carcinogenic and non-carcinogenic effects of various solvents, including trichloroethylene, perchloroethylene, vinyl chloride, 1,1,1-trichloroethane, ethylbenzene, toluene, xylene, and various other solvents in humans and animals.

Evaluation of Acrylamide Toxicity: Critically evaluated the literature on acrylamide, with particular attention to the carcinogenic effects in humans (e.g., epidemiologic studies, adduct formation). In addition, evaluated the literature on potential excess cancer risks associated with exposures to acrylamide in foodstuffs.

Evaluation of Potential Carcinogenicity of “Take-Home” Asbestos Exposure: Evaluation of the animal and epidemiological asbestos literature (brake worker studies) for mesothelioma.

Reactive Airways Dysfunction Syndrome: Reviewed literature for various chemicals, including ammonia and hydrogen sulfide, and their potential association with respiratory effects, including RADS (reactive airways dysfunction syndrome).

Pesticide Toxicity: Critically reviewed and analyzed the literature related to the neurological (e.g., peripheral neuropathy) and neuropsychological (e.g., toxic encephalopathy) effects of various organophosphate (e.g., chlorpyrifos) and carbamate insecticides.

Review of PCB Neurodevelopmental Toxicity: Evaluated the human and animal evidence concerning the neurodevelopment toxicity of PCBs. Evaluated the potential reproductive and developmental effects of different PCB mixtures using federal and state hazard assessment guidelines.

Evaluation of the Carcinogenicity of Chrysotile Asbestos: Reviewed the various issues related to chrysotile asbestos, examining risk assessment approaches used to assess cancer risk, background exposures to fibers, epidemiologic studies of individuals exposed to chrysotile asbestos, and various risk assessment of governmental/agency positions on asbestos.

Welding Exposure Evaluation: Evaluated the toxicity of welding fumes and paint solvents, with an emphasis on the cardiovascular toxicity of these various agents.

Toxicity of Pentachlorophenol: Reviewed the toxicity literature on pentachlorophenol to assess the health effects from potential exposures to pentachlorophenol as a result of residing in a log home.

Effects of Tire-Derived Fuel Burn: Evaluated the adverse effects of inhalation exposure to various compounds (including mercury and zinc) and particulate matter from a tire-derived fuel test burn.

Paints and Asthma: Evaluated the respiratory toxicity of paints and mildewicides to determine whether they were causally associated with asthma.

Neurotoxicity of Carbon Disulfide: Critically evaluated the literature to assess the neurotoxicity of carbon disulfide.

Toxicity of Trichloroethylene (TCE): Conducted a comprehensive critical review of the literature for TCE and various endpoints (e.g., cancer and non-cancer effects, pharmacokinetics, etc._, focusing on animal studies, volunteer studies, and epidemiological studies.

Lead in Drinking Water: Evaluated lead concentrations in “first draw” water.

Toxicity of Carbon Monoxide: Reviewed the carbon monoxide toxicity literature, in particular the literature concerned with the neuropsychological effects of exposure.

Toxicity of X-ray Processing Chemicals: Determined whether certain x-ray processing chemicals (e.g., glutaraldehyde) were causally associated with the so-called “Multiple Chemical Sensitivity” syndrome and pulmonary effects.

Assessment of Exposure to Sodium Pentachlorophenate (Sodium Salt of Pentachlorophenol): Reviewed the toxicological literature to determine whether a causal association exists between sodium pentachlorophenate and reactive airways dysfunction syndrome (RADS).

Solvents and Kidney Disease: Performed a critical evaluation of the literature on the issue of solvent nephropathy. Reviewed epidemiology studies of gasoline, petroleum, painters, printers, and many other solvent-exposed cohorts, as well as case-control studies, registry studies, and meta-analyses of individuals exposed to solvents. In addition, examined issues surrounding biological plausibility.

Evaluation of Ammonia Toxicity: Evaluated the neurotoxicity and pulmonary effects associated with ammonia exposures generated from the removal of sediments from mine waste-stream receiving ponds. Evaluated the acute and chronic effects of ammonia in humans, along with biological exposure data and industrial hygiene data.

Evaluation of Trace Benzene Exposure and Myelodysplastic Syndrome (MDS): Conducted a comprehensive review of the literature related to benzene and MDS from exposure to petroleum-based solvents. Part of this assessment included a review of industrial hygiene measurements.

Sinonasal Cancer and Metals: Identification, retrieval, and organization of scientific literature pertaining to sinonasal cancer and various metals at issue (arsenic, cadmium, hexavalent chromium, and nickel). Researched the etiology and possible causes of sinonasal cancer.

Exposure to Multiple Chemicals and Brain Cancer: Evaluated exposures and carcinogenicity literature of multiple chemicals, including vinyl chloride and acrylonitrile, to assess whether the evidence was sufficient to indicate that these compounds were neurocarcinogenic in humans.

Exposure to Vaporized Petroleum Distillate and Surfactant: Reviewed the toxicological literature (especially respiratory toxicity and neuropsychological related effects) related to vaporization of petroleum distillate/surfactant product added to hot sodium hydroxide. Industrial hygiene sampling data were reviewed as part of the assessment.

Evaluation of Toxicity of Sulfates, Nitrates, and Boron in Groundwater: Reviewed the toxicity of boron in animals and humans via exposure through groundwater. Also, included in the assessment were the effects of these compounds on livestock.

Food Additives and Flavorings

Safety Evaluation of a Food Additive: Reviewed the numerous mechanistic, animal, and epidemiologic studies of various butter flavoring compounds (primarily diacetyl) to evaluate potential pulmonary effects in humans. Evaluated NIOSH Health Hazard Evaluations (HHEs) conducted on worker populations. Evaluated pulmonary function tests results and effects reported. Evaluated potential confounders.

Regulatory History and Gap Assessment of Food Additive: Development roadmap and gap assessment for product to be used for pet and human food use. Evaluated US and European regulatory and toxicology historical documents.

Evaluation of Safety Profile of Herbal Products: Conducted assessments of various herbal products, focusing on chemical identity, historical and present uses, regulatory history, animal and human toxicity data, and data gaps.

Generally Recognized as Safe (GRAS) Assessment: Identified and summarized information on chemical identity, historical and present use, relevant animal and human toxicity data, and data gaps for a product for potential human food use.

Evaluated Hazards of Solvents for Food Use Compounds: Prepared hazard assessment summaries of various solvents for use in food packaging. Reviewed primary and secondary toxicity literature as well as regulatory information on compounds to assess toxicity of identified compounds.

Safety of Farmed vs. Wild Salmon: Evaluated the concentrations of PCBs in farmed and wild salmon compared with the USFDA’s tolerance level.

Consumer and Personal Care Products

Systematic Review of the Safety of Caffeine: Participated in an evidence-based review of the health effects (cardiotoxicity) associated with the consumption of caffeine. Screened relevant articles using DistillerSR.

Laminate and Wood Flooring: Reviewed the potential health effects associated with exposure to laminate and wood flooring. Examined the methods and results of analytical testing on flooring and the regulations for wood flooring, as well as the toxicity of formaldehyde.

Consumer Safety Review: Reviewed the safety of a dye component in a consumer product used by infants and toddlers, as well as adults. Evaluated *in vitro* toxicological studies conducted by outside contract laboratories and produced report summarizing relevant issues for the client.

Evaluation of Potential Effects of Carpet Emissions: Reviewed the toxicity literature on multiple chemicals that were emitted from a carpet product to determine whether they could be the cause of the so-called “Multiple Chemical Sensitivity” syndrome.

Evaluation of a Perfluorinated Acid in Carpet: To address potential concerns from PFOA in carpet-related products, a comprehensive evaluation of PFOA literature was undertaken, including all published and unpublished chemistry, environmental exposure, pharmacokinetic, animal, volunteer, and occupational studies. A 100+ page primer was developed for the client detailing the findings.

Evaluation of Potential Respiratory Toxicity of Paint Solvent Emissions: Evaluated the toxicity and exposure literature regarding whether or not exposure to solvents emitted from a particular paint product could cause or exacerbate asthma.

Review of Toxicity of Portland Cement Concrete: Comprehensive review of the toxicity of the various components of Portland cement concrete. Evaluated a case of potential over-exposure to Portland cement via the dermal route.

Review of Malathion Toxicity: Conducted a review of the general toxic effects that would be expected from exposure to malathion following its use as a general insecticide.

Evaluation of the Carcinogenicity of Benzene, Trichloroethylene (TCE), and 1,1,1-Trichloroethane (TCA) and Brain Cancer: Evaluated the animal and epidemiological literature to determine whether exposure to these solvents from a hot glue product were causally associated with brain cancer. Chemical testing on the glue product was conducted and results evaluated to assess other potential exposures.

Review of the Acute Toxicity of Gasoline Exposure: A review of the published literature was undertaken to determine the health effects of an acute exposure to gasoline.

Aplastic Anemia and Exposure to Art Products: Causal evaluation of aplastic anemia and various products reportedly present in art product supplies at an art school. The animal and human toxicity of the following chemicals were researched: the benzene metabolites hydroquinone and benzoquinone; glycol ethers; and mixed petroleum solvents (e.g., Stoddard solvent, kerosene, and naphtha).

Evaluation of Solvent-Related Renal Disease: Reviewed relevant published literature to determine whether there was a causal relationship between exposure to various solvents utilized in the printing industry and renal failure.

Evaluated Safety of Plant Emissions: Evaluated the potential adverse effects from low-level emissions of various aldehydes and ketones emitted from a plant.

Toxicity of Nail Products: Reviewed the respiratory, neurological, and cardiovascular toxicity from exposure to ethyl methacrylate as a component of nail products.

Photocopying Chemicals Toxicity Review: Reviewed the toxicity and possible health effects of exposure to multiple photocopying chemicals. Included in the review was an evaluation of the levels of exposure that might exist for individuals working near photocopying machines.

Pesticide Product Evaluation: Evaluated the teratogenicity of a termiticide (active ingredient chlorpyrifos) in animals and humans.

Toxicity of Materials in Lighting Ballasts: Conducted a review of the toxicity of materials related to ballast lighting and materials that might be emitted from an over-heated ballast (e.g., asphalt, carbon monoxide, PAHs), in particular, the respiratory and neurological toxicity of these compounds.

Evaluation of Odo-Ban®: Evaluated the potential inhalation toxicity of the active ingredient in Odo-Ban®, benzalkonium chloride.

General Pesticide Experience: Evaluated the toxicity of numerous pesticides, including acephate, atrazine, azinphos-methyl, biological compounds (e.g., *Bacillus thuringiensis*, rotenone), carbaryl, chlorothalonil, 2,4-dichlorophenoxyacetic acid (2,4-D), DDT, chromated copper arsenate (CCA), chlorpyrifos, diazinon, dicamba, dimethoate, diquat, heptachlor, glyphosate (Roundup®), limonene, malathion, methyl bromide, paraquat, pentachlorophenol, picloram, propoxur, permethrin, and simazine.

Pharmaceutical Agents and Medical Devices

Safety Assessment of Excipients Used in Pharmaceutical Products: Evaluated the pharmacokinetic and animal and human toxicity data related to excipient compounds.

Teratogenicity of Clomid: Evaluated potential adverse effects of the fertility drug clomiphene citrate and its ability to cause birth defects.

L-tryptophan: Critically evaluated the literature pertaining to eosinophilia myalgia syndrome (an eosinophil excess) that resulted from contaminants in an over-the-counter amino acid sleep aid.

Evaluation of an Herbal Supplement Product: Evaluated various components of an herbal supplement that contained ephedra, caffeine, and other compounds with respect to mechanism of action and possible side effects. Reviewed the pharmacokinetics of these compounds and doses associated with toxicity.

Assessment of Side Effects of a Popular Over-the-Counter Medication: Conducted detailed assessment of pharmacologic, toxicologic, and pharmacoepidemiologic literature concerning a common over-the-counter medication to determine whether Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) was causally associated with the product.

Evaluation of Pharmaceutical Product for Potential Cardiovascular Side Effects of Phenylpropanolamine: Participated in a review of the published and unpublished literature to determine whether a causal relationship exists between popular cough-and-cold preparations containing phenylpropanolamine (PPA) and strokes.

Evaluation of the Safety Profile of a Pharmaceutical Product: Evaluated the acute, chronic, and carcinogenicity safety profile of metronidazole for a prospective buyer of a company manufacturing this product.

Tamoxifen: Assisted in the editing and managing of the supplement “Scientific Review of Tamoxifen” for the journal *Seminars in Oncology*.

Evaluation of a Medication Adverse Effect: Conducted a comprehensive review of the literature on prednisone and conducted a dose-response analysis to determine whether the compound could be responsible for the specific side effect of avascular necrosis.

Safety Evaluation of a Nasal Spray Product: Participated in a safety evaluation of a nasal product containing zinc. Evaluated historical as well as recent safety data on the product.

Regulatory Compliance

Evaluation of Respiratory Regulatory Limit for Caprolactam: Conducted an extensive review of the chemical and pharmacokinetic properties of caprolactam, as well as the toxicity of this compound in animals and humans, in response to proposed California's OEHHA Reference Exposure Levels (RELs). Prepared rebuttal comments to OEHHA in response to these proposed RELs.

Preparation of Comments for Submittal to ATSDR: Participated in project that consisted of a review of the human clinical and epidemiological data on PCBs. Developed a 100+-page document for the client to submit to ATSDR's Draft Toxicological Profile for PCBs Update.

Review of Allowable Effluent Concentration for d-Limonene. Reviewed the applicability of a city government's allowable effluent concentration of d-limonene. Evaluated ecological testing data in support of this risk assessment.

Review of Manganese Water Standard: Conducted a critical review of studies that were being considered in support of a standard for manganese in potable water.

Derivation of Toxicity Constants for 1,1-Dichloroethylene (VDC): Participated in benchmark dose (BMD) derivation and calculation of acceptable indoor air exposure levels for VDC based on the BMD approach for the Colorado Department of Transportation.

Site Assessments/Risk Assessments

Risk Assessment for Chemicals Used in a Fire Suppression System: Evaluated the potential toxicity to human health and potential for damage to possessions from possible contact with water and/or residues that might contain products used in a fire suppression system.

Risk Assessment for Hexavalent Chromium and Trichloroethylene (TCE) at a Site in California: Calculated inhalation and ingestion short-term and lifetime risks for exposures to CrVI and TCE. This evaluation included a review of the recent literature on the relevant toxicological endpoints at issue.

Risk Assessment of Trichloroethylene from Vapor Intrusion: Assessed exposure, as well as the theoretical risks associated with these exposures, to trichloroethylene via inhalation from vapor intrusion in a home basement.

Exposure and Risk Assessment of Site in Utah: Evaluated the non-carcinogenic and carcinogenic risks posed by calculated levels of exposure to arsenic, cadmium, copper, lead, and nickel present in site soil.

Evaluation of Human Health Effects from Munitions Plant Emissions: Reviewed the human health effects of RDX, MNRDX/DNRDX/TNRDX, dimethylnitrosamine, hydrazine, and dimethyl-hydrazines potentially associated with emissions from a munitions plant in Utah.

Review of the Toxicity of Trichloroethylene (TCE), Chromium, and 1,1-Dichloroethylene (DCE): Undertook a comprehensive review of the toxicological literature on TCE, chromium, and 1,1-DCE (chemicals present as drinking-water contaminants near an airport) to assess their potential cancer and non-cancer effects.

Assessment of PCB Exposure at State Building: Participated in an assessment of the potential health effects associated with exposure to PCBs (and combustion products) resulting from a fire that occurred at a State building in Pennsylvania. Determined a surface cleanup level that would render the building safe for long-term occupancy.

Evaluation of Vinyl Chloride (VC) Carcinogenicity: Conducted an assessment of the animal and epidemiologic evidence to determine whether a causal association exists between vinyl chloride and liver or brain cancer among individuals exposed to VC in the environment.

Toxicity of Acetaldehyde: Conducted a thorough review of the non-cancer and cancer effects of exposure to acetaldehyde resulting from a train derailment in West Virginia.

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Toxicity Assessment and Toxicity Profile Generation for Former Electronics Site (Seminole County, Florida): Reviewed the toxicity of multiple chemicals for multiple diseases. Generated toxicity profiles for benzene, Freon, lead, methylene chloride, rosin, 1,1-dichloroethylene, 1,1,1-trichloroethane, trichloroethylene, toluene, 1,4-dioxane, and vinyl chloride. Provided thorough research regarding confounders for over 30 cancer and non-cancer conditions.

Risks from Acute Spill of Coal Tar Light Oil (CTLO): Evaluated the risks from an acute CTLO spill from a tanker. Considered the potential toxicities and risks associated with the components of CTLO spills for the vicinity surrounding the spill. Readings taken near the time of spill were considered as part of the analysis.

Miscellaneous Projects

Evaluation of a Possible Cancer Cluster: Studied potential cancer clusters and whether these were related to environmental exposures to dioxin (TCDD).

Risk Communication Services at a Public Meeting: Provided risk communication and toxicology support at a public meeting regarding issues related to phosphogypsum.

Risk Communication Services at a Public Meeting: Provided risk communication services at a public meeting, discussing the use of a chlorophenoxy herbicide in a Florida waterway.

Historical Perspective of PCB: Provided a historical perspective on the toxicological properties of PCBs, showing how this knowledge developed over the years (~1929–2010).

Medical Monitoring Program Rebuttal: Researched recommendations for and against various medical monitoring protocols for multiple diseases and cancers from several major medical and scientific organizations and agencies. Researched the criteria that have been proposed by various scientific, medical, and regulatory bodies as being appropriate and necessary prior to instituting a medical monitoring program. Calculated excess cancer rates from the use of various diagnostic techniques that required the use of radiation.

Lead Toxicity Presentations: Summarized the regulatory standards for lead and the toxicity of lead based on target organs and presented the information to companies at their request.

PUBLICATIONS

Wikoff DS, Urban JD, Ring C, **Britt J**, Fitch S, Haws LC. 2020. Development of a range of plausible non-cancer toxicity values for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) based on effects on sperm count: Application of systematic review methods and quantitative integration of dose response using meta-regression. Toxicol Sci 179(2):162-182, https://doi.org/10.1093/toxsci/kfaa171.

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BOOK CHAPTERS

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SEMINARS AND CONTINUING EDUCATION

Introduction to the Fundamentals of Epidemiology. London School of Hygiene and Tropical Medicine. 2012.

Society of Toxicology Meeting Continuing Education Courses: (1) Toxicology of Pesticides; (2) Risk Assessment, (3) Methods for Assessment of Neurotoxicity, (4) Comparative Endocrine Toxicology; and (5) Evaluating Toxicity of Engineered Nanomaterials: Issues with Conventional Toxicology Approaches; and (6) Protecting Human Health: Use of Toxicological and Epidemiological Data in Determining Safe Levels for Human Exposure.

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Florida State University Center for Biomedical and Toxicological Research, and multiple other state and federal agencies. Mercury Contamination in Florida: Impacts and Solutions. Tallahassee, FL. June 1990.

BRITT

EXHIBIT B

Testimony Experience of Janice K. Britt, Ph.D.
2016-2021

1. Clayton Bache v. TIC-Gulf Coast
   Deposition Testimony - North Carolina Industrial Commission [April 2016]
   Raleigh, NC

2. Jaimie Bibby and Cole Solis v. The Falls Joint Venture-R, LLC, Troon Golf, LLC, and Brett Stephen Hughett
   Deposition Testimony - District Court [October 2016]
   Fayette County, TX

3. James and Mary Philpott v. Kansas City Power and Light Company, et al.
   Deposition [July 2016] and Trial Testimony [September 2016] - 27^{th} Judicial Circuit
   Henry County, MO

4. Manatee County Commission, Mosaic Proposal to Expand Mining Operations
   Hearing Testimony [February 2017]
   Manatee County, FL

5. Teddy Scott and Melanie Scott v. Dyno Nobel, Inc.
   Deposition Testimony [March 2018]
   U.S. District Court for the Eastern District of Missouri

BRITT

EXHIBIT C

Below is my fee schedule:

1) $480/hour for all work
2) $235/hour for travel time

Exhibit E

Defendants' thirty days to designate Exhibit E as confidential has not elapsed. In accordance with the Court's Confidentiality and Protective order, Plaintiffs will forward the Exhibit to the Court directly via email for its in camera review.

Exhibit F

Regulatory Toxicology and Pharmacology **35,** 44–55 (2002)
doi:10.1006/rtph.2001.1518, available online at http://www.idealibrary.com on IDEAL®

Evaluation of the Carcinogenicity of 1,1-Dichloroethylene (Vinylidene Chloride)[1]

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The U.S. Environmental Protection Agency has classified 1,1-dichloroethylene (vinylidene chloride; VDC) as a "C" carcinogen and has developed an inhalation unit risk value and an oral cancer slope factor for this chemical. The development and use of these cancer potency estimates for risk assessment purposes are questionable. The inhalation unit risk value is based on increased kidney adenocarcinomas in Swiss mice from one study. This type of cancer was not increased in female mice or in rats or hamsters in the same study nor in male mice of a similar strain in another study with higher VDC exposures. The VDC oral cancer slope factor is based on a non-statistically significant increase in adrenal pheochromocytomas in male rats following oral exposure in a standard National Toxicology Program chronic bioassay. Both human and animal literature relevant to VDC carcinogenicity was reviewed according to the USEPA draft *Guidelines for Carcinogen Risk Assessment* with the objective of determining the weight-of-evidence for VDC carcinogenicity. We conclude that information currently available for VDC is most appropriately characterized in a weight-of-evidence narrative by the descriptor "inadequate for an assessment of human carcinogenic potential." For chemicals with this descriptor, dose–response assessment is not indicated. Under this guidance, quantitative estimates of cancer risks associated with VDC exposure are inappropriate until additional, more definitive evidence for human carcinogenicity becomes available. © 2002 Elsevier Science (USA)

***Key Words*: vinylidene chloride; 1,1-dichloroethylene; 1,1-dichloroethene; carcinogenicity; risk assessment.**

INTRODUCTION

1,1-Dichloroethylene (CAS No. 75-35-4), commonly known as vinylidene chloride (VDC), is a volatile liquid that has been used as a chemical intermediate in the production of 1,1,1-trichloroethane and as a monomer in commercial resins and packaging materials. VDC is also an environmental degradation product of several chlorinated solvents (e.g., trichloroethylene, tetrachloroethylene, and 1,1-dichloroethane) and can be found at sites contaminated with these solvents (Coleman *et al.*, 1977; Fishbein, 1979; Wallace *et al.*, 1986). VDC is a central nervous system depressant in humans when inhaled (USEPA, 1979) and repeated exposure to low concentrations of VDC may cause liver and renal dysfunction in humans (Torkelson and Rowe, 1981). In laboratory animals, liver, kidney, and lung are the major target organs for VDC toxicity following acute and chronic inhalation exposure (Gage, 1970; Short *et al.*, 1977; Reitz *et al.*, 1980; Plummer *et al.*, 1990).

The potential carcinogenicity of VDC has been evaluated in several laboratory animal species by a number of routes of exposure (Maltoni, *et al.*, 1977, 1982, 1985; Viola and Caputo, 1977; Lee *et al.*, 1978; Van Duuren *et al.*, 1979; Hong *et al.*, 1981; NTP, 1982; Quast *et al.*, 1983). Significant increases in some tumor types were observed in a few of these studies, but these were not confirmed in other studies of VDC exposure using the same species. Noting weaknesses in many of these studies, the USEPA considered the weight-of-evidence for VDC consistent with classification in category C—a possible human carcinogen. An inhalation unit risk factor for VDC (5×10^{-5} per $\mu g/m^3$) was developed using the linearized multistage (LMS) procedure applied to data showing a significant increase in kidney adenocarcinomas in male Swiss mice exposed to VDC by inhalation for 12 months (data from Maltoni *et al.*, 1977, 1985). An oral cancer slope factor for VDC (0.6 per (mg/kg)/day) was derived from data on the incidence of adrenal pheochromocytomas in male F344 rats treated with VDC by gavage for 24 months (NTP, 1982). This oral cancer slope factor is unusual in that it is based on tumor incidences that were not significantly increased above controls. The USEPA has justified their derivation of a slope factor under these circumstances by stating that the oral cancer slope factor for these tumors is within a factor of 2 of the oral cancer slope

[1] This analysis was initiated at the request of Walsh Environmental Scientists and Engineers, Inc. The analysis was conducted independently and without compensation, and the opinions expressed herein are solely those of the authors.

0273-2300/02 $35.00

factor that could be derived from the VDC inhalation data of Maltoni *et al.* (1977, 1985). (The oral unit risk for VDC in drinking water is 1.7×10^{-5} per microgram per liter based on the negative NTP data and 3.3×10^{-5} based on the Maltoni *et al*. inhalation studies; USEPA, 1985).

Nearly 5 years ago, the USEPA developed draft *Guidelines for Carcinogen Risk Assessment* (USEPA, 1996). These guidelines were intended to improve upon previous guidance (i.e., USEPA, 1986) and offer a new weight-of-evidence classification system for potential human carcinogenicity. Although these guidelines have not yet been formally accepted by the USEPA, the most recent version of these guidelines (USEPA, 1999) is being used nonetheless in certain situations in anticipation of their approval. In this analysis, we explore application of the principles and procedures in these guidelines to an evaluation of the carcinogenicity of VDC. Specifically, we have critically evaluated the literature relevant to VDC carcinogenicity and the weight of evidence for its human carcinogenic potential using the criteria described in these guidelines.

THE CARCINOGENIC POTENTIAL OF VDC IN ANIMALS

Studies examining the carcinogenic potential of VDC in animals are summarized in Table 1.

Summary of the results obtained from inhalation studies. Viola and Caputo (1977) reported results of two studies of VDC carcinogenicity in rats. In one study, male and female Wistar rats were exposed to VDC vapor at concentrations of 200 ppm for the first 5 months and 100 ppm thereafter for 4 h/day, 5 days/week, for 12 months. Abdominal tumors characterized as "reticulum cell sarcomas of a nonscincytial type" were found in 14% of VDC-treated males and 35% of females exposed to VDC. However, the same tumors were observed in controls at a similar incidence (17% in males and 30% in females). In the second study, Sprague–Dawley rats were exposed to 75 and 100 ppm VDC (exposure protocol not reported). No increase in tumors compared with controls was observed. No statistical analysis of the data is reported for this study.

Maltoni *et al*. (1977, 1985) conducted several experiments to assess potential VDC carcinogenicity. In one experiment (designated BT401 by the authors), male and female Sprague–Dawley rats were exposed by inhalation to 10, 25, 50, 100, or 150 ppm VDC for 4 h/day, 4–5 days/week, for 52 weeks. The authors originally used 200 ppm as the highest VDC concentration, but reduced it to 150 ppm due to toxicity. On occasion, toxicity forced the use of four exposures per week rather than the intended five per week. The presence or absence of tumors in each animal was determined after spontaneous death. Total mammary tumor incidence was increased in some VDC-treated groups of females, but not others, with no apparent dose–response trend. The incidence of malignant mammary tumors was less in all treated groups than the controls. No increases in tumors at other sites in VDC-treated rats were reported in this study.

In a separate publication (Maltoni *et al*., 1982), the incidence of brain tumors is reported for Sprague–Dawley rats exposed to VDC under conditions as described above. It is unclear whether these data are derived from their BT401 experiment or another, separate experiment with the same exposure frequency, duration, and VDC concentrations. Brain tumors were observed in five of the rats exposed to 50 ppm and four of the control rats. The number of animals with brain tumors in all of the remaining treatment groups was one or less. The highest concentration group, 100 ppm, had no animals with brain tumors.

In another experiment (designated BT402), mice were exposed via inhalation to 10 or 25 ppm VDC for 4 h/day, 4–5 days/week, for 52 weeks (Maltoni *et al*., 1977, 1985). Originally, the study also included a group treated with 50 ppm VDC, but this was discontinued due to excessive toxicity. As with the BT401 experiment, statistical methods and the basis for determining statistical significance were not described. Among male mice exposed to 25 ppm VDC (two groups combined), 23.5% had kidney adenocarcinomas, as opposed to 0% in the controls. These tumors were not observed in male mice exposed to 10 ppm VDC and were reported as not significantly elevated in females. Significant increases in mammary carcinomas were reported for female Swiss mice at 10 and 25 ppm, although the response was greater at 10 than 25 ppm. Also, significant increases in pulmonary adenomas were reported for male Swiss mice exposed to 10 or 25 ppm and in females exposed to 25 ppm. In yet another experiment (designated BT405), Chinese hamsters were exposed to 25 ppm for 4 h/day, 4–5 days/week, for 52 weeks. No increases in tumor incidence were observed at any sites in this experiment.

Lee *et al*. (1978) exposed CD-1 mice and CD rats to 55 ppm VDC for 6 h/day, 5 days/week, for 12 months. Six of 35 VDC-exposed male mice developed bronchioalveolar adenoma compared with 1 in control male mice. No bronchioalveolar adenomas were observed in either treated or control female mice. One female and 2 male mice developed liver hemangiosarcomas, while none were observed in either male or female controls. None of the tumor incidences were significantly different from controls. Two of 36 male rats exposed to VDC developed hemangiosarcomas of the mesenteric lymph nodes and subcutaneous tissues, but this tumor incidence was not statistically different from that of the unexposed controls.

In a follow-up study, CD-1 mice were exposed to 55 ppm VDC for 6 h/day, 5 days/week for 1, 3, or

TABLE 1
Summary of 1,1-Dichloroethylene Cancer Studies

Study	Species, strain, and gender	Dosing regimen	Results	Comments
		Inhalation exposure		
Viola and Caputo (1977)	Male and female Wistar rats	200 ppm VDC for 5 months and 100 ppm thereafter; 4 h/day, 5 days/week, for 12 months.	Similar incidence of "*reticulum cell sarcomas of a nonscincytial type*" in exposed and control rats.	No statistical analysis was reported for this study. The authors concluded that there was no observable correlation between tumor formation and VDC exposure.
	Male and female Sprague–Dawley rats	75 or 100 ppm VDC; details of exposure not specified.	Controls had similar or higher incidence of subcutaneous fibromas and abdominal lymphomas than exposed rats.	
Maltoni *et al.* (1977, 1985)	Male and female Sprague–Dawley rats	10, 25, 50, 100, or 150 ppm VDC, 4h/day, 4–5 days/ week, for 52 weeks;[a] the presence or absence of tumors was assessed at spontaneous death.	Mammary tumor incidence was increased in females in some treatment groups, but not in a dose-related manner. The incidence of malignant mammary tumors was less in all treated groups than controls.	This experiment was designated BT401 by the authors. Statistical methods were not described.
	Male and female Swiss mice	10 or 25 ppm VDC, 4–5 days/ week, for 52 weeks;[b] mice were held until the end of the experiment at week 126. The presence or absence of tumors was assessed at spontaneous death.	28/119 male mice exposed to 25 ppm developed kidney adenocarcinomas vs 0/126 controls; increases in mammary and pulmonary adenomas were also reported, but the incidence was not dose related.	This experiment was designated BT402 by the authors. Statistical methods were not described. The authors attributed the increase in kidney adenocarcinomas to VDC exposure.
	Male and female Chinese hamsters	25 ppm VDC for 4 h/day, 4–5 days/week, for 52 weeks. The presence or absence of tumors was assessed at spontaneous death.	No increases in tumor incidence were observed at any site.	This experiment was designated BT405 by the authors. Statistical methods were not described.
Maltoni *et al.* (1982)	Male and female Sprague–Dawley rats	10, 25, 50, 100, or 150 ppm VDC, 4 h/day, 4–5 days/week, for 52 weeks.	The incidence of brain tumors in animals exposed to 50 ppm VDC was similar to controls. Other treatment groups had lower brain tumor incidences.	No statistical methods are described. The increase in tumors did not appear to be dose related.
Lee *et al.* (1978)	Male and female CD-1 mice	55 ppm VDC, 6 h/day, 5 days/ week, for 12 months.	Bronchioalveolar adenomas occurred in 6/35 male mice versus 1/26 in controls and none in treated or control females. Liver hemangiosarcomas occurred in 1 female and 2 male mice versus none in male or female controls.	None of the tumor incidences were statistically significantly different from controls.
	Male and female CD rats	55 ppm VDC, 6 h/day, 5 days/ week, for 12 months.	Hemangiosarcomas of the mesenteric lymph nodes and subcutaneous tissue occurred in 2/36 male rats versus 0/35 of controls.	None of the tumor incidences were statistically significantly different from controls.
Hong *et al.* (1981)	Male and female CD-1 mice	55 ppm VDC, 6 h/day, 5 days/ week, for 1, 3, or 6 months, followed by a 12-month recovery period.	Hepatocellular tumors occurred in 4/28 male mice compared to 10/60 for controls. Bronchioalveolar tumors were observed in 5/56 males and females compared to 16/120 for controls.	For both species, there were no statistically significant increases in observed tumor incidences. The authors commented that tumors appeared to be age-related, spontaneous tumors unrelated to VDC exposure.
	Male and female CD rats	55 ppm VDC 6 h/day, 5 days/ week, for 1, 3, 6, or 10 months, followed by a 12-month recovery period.	One male rat developed hemangiosarcoma, while none were observed in the control group. Fibroadenomas were observed in females (5/36); however, the incidence was the same as the control group.	

TABLE 1—*Continued*

Study	Species strain, and gender	Dosing regimen	Results	Comments
Quast *et al.* (1986)	Male and female Sprague–Dawley rats	25 or 75 ppm VDC for 6 h/day, 5 days/week, for 18 months, with interim sacrifices at 1, 6, and 12 months.[c] Animals surviving at 18 months were euthanized at 24 months.	Mammary adenocarcinomas were significantly increased in female rats at 25 ppm, but not 75 ppm. Several other tumor types were significantly decreased in VCD-treated rats.	The mammary adenocarcinoma incidence observed at 25 ppm was within the range of historical controls. The authors concluded that the increase was not attributable to VDC exposure.
Cotti *et al.* (1988)	Pregnant, Sprague–Dawley rats	100 ppm, 4 h/day, 5 days/week for 7 weeks, beginning on the 12th day of gestation; after 7 weeks, exposure was continued for 7 h/day, 5 days/week for 97 weeks for a total exposure duration of 104 weeks. Offspring were subjected to the same exposure regimen above beginning *in utero* and lasting into adulthood for a total duration of either 15 or 104 weeks.	Among offspring exposed for 104 weeks beginning *in utero*, an increased incidence of malignant tumors and leukemias compared to controls was reported.	No statistical analysis was conducted on the data.
		Oral exposure		
Ponomarkov and Tomatis (1980)	Female BD IV rats	150 mg/kg VDC via gavage on day 17 of gestation; offspring of these animals were administered weekly doses of 50 mg/kg; surviving animals terminated at 120 weeks or when moribund.	The authors report that no significant differences in tumor incidence between treated animals and controls were observed.	No statistical methods are described.
Maltoni *et al.* (1977, 1985)	Male and female Sprague–Dawley rats.	5, 10, or 20 mg/kg VDC,4–5 days/week, for 12 months; an additional experiment following the same protocol was conducted at 0.5 mg/kg.	The authors report that no statistically significant increases in tumor incidence were observed in any of the VDC treatment groups.	No statistical methods are described. These experiments are designated BT 403 and BT 404 by the authors.
Maltoni *et al.* (1982)	Male and female Sprague–Dawley rats.	0.5, 5, 10, or 20 mg/kg VDC, 4–5 days/week for 52–59 weeks.	No dose-related trends in brain tumor incidence were observed.	
NTP (1982)	B6C3F1/N mice	0, 2, or 10 mg/kg via gavage, 5 days/week, for 104 week.	The only significant increases in tumors were for "lymphoma" or "lymphoma or leukemia" among mice treated with the low dose (2 mg 1 kg). This effect was not seen among high-dose females or among VDC-exposed male mice or male or female rats.	Due to the sex dependency and lack of dose response with respect to the increase in lymphomas, the report concluded VDC was not carcinogenic for F344/N rats or B6C3F1 mice of either sex under the conditions of the bioassay.
	F344/N rats	0, 1, or 5 mg/kg via gavage, 5 days/week 104 weeks.		
Quast *et al.* (1983)	Female, Sprague–Dawley rats	50, 100, or 200 ppm in drinking water *ad libitum* for 2 years; estimated dosages were 0, 7, 10, or 20 mg/kg/day for males and 0, 9, 14, or 30 mg/kg/day for females.	A statistically significant increase in the incidence of combined mammary gland fibroadenomas and adenofibromas was reported for females in the 50 ppm (7 mg/kg/day) group.	Because the incidence was within the normal range of the historical control data and the effect was not dose related, the authors concluded that this finding was not related to the ingestion of VDC.

[a] The study originally included a group treated with 200 ppm, but this was discontinued due to toxicity.
[b] Originally the study included a group treated with higher concentrations, but this was discontinued due to excessive toxicity.
[c] Initially, the exposure concentrations used in the study were 10 and 40 ppm. Based on the lack of treatment-related effects in animals at the 1-month sacrifice, the concentrations were increased to 25 and 75 ppm for the remainder of the study.

6 months followed by a recovery period of 12 months (Hong *et al.*, 1981). CD rats were similarly exposed for 1, 3, 6, or 10 months followed by a 12-month recovery period. Tumor incidences were greater than controls for some tumor types, but none was significantly increased.

Quast *et al.* (1986) exposed male and female Sprague–Dawley rats to 25 and 75 ppm VDC for 6 h/day, 5 days/week, for 18 months, with interim sacrifices at 1, 6, and 12 months. Animals surviving after 18 months of VDC exposure were allowed to recover until 24 months. Initially, the concentrations to be evaluated in this study were 10 and 40 ppm. However, due to the lack of treatment-related effects at the 1-month interim sacrifice, the concentrations were increased to 25 and 75 ppm. Several tumor types were significantly decreased in VDC-treated rats. The incidence of mammary adenocarcinomas among female rats (7 of 86 rats) exposed to 25 ppm VDC was significantly higher than in controls (2 of 84 rats). Among female rats exposed to 75 ppm VDC, the incidence of mammary adenocarcinomas (4 of 84) was not significantly increased. The tumor incidence at the lower exposure was noted by the authors to be within the range of historical controls. This, coupled with the absence of a response at the higher VDC concentration, led the authors to conclude that the increase in mammary adenocarcinomas was not attributable to VDC exposure.

Cotti *et al.* (1988) exposed pregnant female Sprague–Dawley rats to 100 ppm VDC for 4 h/day, 5 day/week, for 7 weeks, beginning on the 12th day of gestation. After 7 weeks, exposure to the same concentration was continued for 7 h/day, 5 days/week for 97 weeks, for a total exposure duration of 104 weeks. Offspring from the dams were also exposed to 100 ppm according to the same regimen for a total exposure duration (beginning *in utero*) of 15 or 104 weeks. The authors reported that rats treated for 104 weeks beginning *in utero* had, as a group, an increased percentage of animals with malignant tumors and an increase in the incidence of leukemias, compared with controls. It is not clear whether these increases are statistically significant, since no statistical analysis is presented.

Summary of the results obtained from oral studies. Ponomarkov and Tomatis (1980) administered a single dose of 150 mg/kg VDC via gavage to a group of 24 female BD IV rats on day 17 of gestation. Offspring (89 males and 90 females) were then given weekly doses of 50 mg/kg VDC via gavage for 120 weeks or until moribund. Controls received vehicle (olive oil) according to the same regimen. The authors reported that no tumor types were significantly increased in either the female rats receiving a single VDC dose or their progeny exposed for 120 weeks. No description of the statistical tests or their results is provided.

Maltoni *et al.* (1977, 1985) treated male and female Sprague–Dawley rats with 5, 10, or 20 mg/kg VDC daily by gavage, 4–5 days/week for 12 months. An additional experiment also examined the effect of a lower dose of VDC, 0.5 mg/kg, following the same exposure protocol. The authors indicated that no significant increases in tumor incidence were observed in any of the VDC treatment groups. No description of the statistical tests or their results was included in this report. A separate publication (Maltoni *et al.*, 1982) provides data on the incidence of brain tumors among Sprague–Dawley rats given 0.5, 5, 10, or 20 mg/kg VDC daily by gavage, 4–5 days/week for 52–59 weeks. No dose-related trends were observed; in fact, the high-dose group had no brain tumors while 11 brain tumors were found in the control animals. For the remaining VDC dose groups the number of brain tumors was 3 or less, and the final incidence of brain tumors was not significantly different from that of the control animals for any dose group.

The National Toxicology Program (NTP) also examined VDC carcinogenicity following oral exposure (NTP, 1982). Male and female B6C3F1/N mice were given 0, 2, or 10 mg/kg VDC by gavage, 5 days/week for 104 weeks. Also, groups of male and female F344 rats were administered 0, 1, or 5 mg/kg VDC by gavage, 5 days/week for 104 weeks. There was a significant increase in the incidence of lymphoma among female mice receiving 2 mg/kg VDC (9/49 compared to 2/48 for controls) and “lymphoma or leukemia” among females at the same dose (15/49 compared to 7/48 for controls; $P = 0.028$). However, this effect was not observed in the high-dose females or among VDC-exposed male mice or rats. Thus, NTP concluded that the lymphomas and leukemias were not related to VDC exposure. Among male rats, adrenal pheochromocytomas were observed in 6/50 (12%) of the vehicle-treated controls, 5/48 (10%) of the rats treated with 1 mg/kg, and 13/47 (28%) of rats treated with 5 mg/kg. Comparison of the high-dose group with controls yielded a P value of 0.045 by Fisher exact test and the Cochran–Armitage test for linear trend was significant with a $P = 0.01$. However, analysis of the data by life table methods found no statistically significant results. Overall, NTP concluded that VDC “administered by gavage was not carcinogenic for F344/N rats or B6C3F1/N mice of either sex” but cautioned that the use of a maximally tolerated dose was not clearly demonstrated in this study.

In a 2-year study by Quast *et al.* (1983), doses of 7, 10, and 20 (mg/kg)/day and 9, 14, and 30 (mg/kg)/day were administered in the drinking water of male and female Sprague–Dawley rats, respectively. Interim results for this study were discussed in Rampy *et al.* (1978). A statistically significant increase ($P < 0.05$) in the incidence of combined mammary gland fibroadenomas and adenofibromas was noted in the females that had received 7 (mg/kg)/day VDC. Because the incidence of these types of tumors was within the normal range of historical control data, and because these tumors were not observed in the higher-dose females or in exposed

males, the authors did not consider the increase in tumor incidence to be attributable to VDC ingestion.

THE RESULTS OF EPIDEMIOLOGY STUDIES

Ott *et al*. (1976) reported the results of a study of cancer mortality in a population of 138 workers exposed occupationally to VDC. In this study, mortality and clinical parameters (serum enzymes indicative of liver injury) were investigated in employees exposed to measured levels of VDC. Estimated time-weighted average VDC concentrations in air ranged from below 5 to 70 ppm, depending upon job type. There were no significant increases in cancer attributable to VDC in the employee population. This study, although negative, involved a small population and the follow-up was incomplete. Also, nearly 40% of the workers had less than 15 years' latency since first exposure.

In a study of 629 workers in Germany occupationally exposed to VDC, there were 7 deaths from cancer (5 bronchial carcinomas) (Thiess *et al*., 1979). However, this number was not in excess of the expected mortality value for this population. Waxweiler *et al.* (1981) found an excess of lung cancer among 556 deaths in a population of workers in a synthetic plastics plant, but this excess was not associated with VDC exposure.

A WEIGHT-OF-EVIDENCE ANALYSIS USING RECENT USEPA GUIDANCE

The USEPA has identified several factors that should be evaluated when determining the weight-of-evidence for a chemical's carcinogenic potential (USEPA, 1999). These include the availability of information regarding carcinogenicity from epidemiological studies of exposed populations; the results of well-conducted cancer bioassays in laboratory animals; and additional, key data. Key data may include evidence for genotoxicity, the carcinogenicity of structurally related compounds, and comparative pharmacokinetic and metabolism information. Based on the weight given these different pieces of information and the coherence of the total evidence, a specific descriptor is then selected that best summarizes and characterizes the carcinogenic hazard posed by the chemical. Basic descriptors include:

"Carcinogenic to humans." This descriptor is used when there is convincing epidemiological evidence for carcinogenicity. In the absence of such evidence, this descriptor is used when there is compelling evidence of carcinogenicity in animals, the mode of carcinogenic action has been identified and is relevant to humans, and key events associated with this mode of action have been observed in exposed human populations.

"Likely to be carcinogenic to humans." This descriptor is used when epidemiological data indicate an association between exposure and cancer, and this is supported by strong experimental evidence of carcinogenicity in animals. If human data are absent, this descriptor is used when the mode of carcinogenic action in animals is known or assumed to be relevant to humans.

"Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential." This descriptor is applied when carcinogenicity data are suggestive but inconclusive. For example, this descriptor would be applicable in situations where increased tumor incidence is marginal or is observed only in a single study. According to EPA guidelines, dose–response assessment is not indicated for chemicals with this descriptor.

"Data are inadequate for an assessment of human carcinogenic potential." As the name implies, this descriptor applies when data are lacking or when existing data are conflicting.

"Not likely to be carcinogenic to humans." This descriptor is applied based on the existence of adequate studies in humans or animals indicating the absence of a carcinogenic effect. This descriptor is also applied in situations where a carcinogenic effect has been observed in animals, but is known to occur by a mode of action not relevant to humans or only in doses greater than humans will encounter.

Information relevant to a weight-of-evidence analysis for VDC carcinogenicity is summarized and critically evaluated in the following sections.

Human Data

Three reports in the literature provided cancer mortality information for VDC-exposed workers (Ott *et al*., 1976; Theiss *et al*., 1979; Waxweiler *et al*., 1981). Although no increases in tumor incidence were associated with VDC exposure in each of these studies, the cohort sizes were small and the observation periods were generally too short to adequately address latency. Given these limitations, the human data are inadequate for assessing the human carcinogenic potential of VDC. The same conclusion was reached by the USEPA and ATSDR in their reviews of the VDC carcinogenicity literature (ATSDR, 1994; USEPA, 1998).

Animal Data

Among four chronic cancer bioassays of VDC in rats (Ponomarkov and Tomatis, 1980; Maltoni *et al*., 1977, 1985; NTP, 1982; Quast *et al*., 1983) and one in mice (NTP, 1982), none showed a significant increase in tumors attributable to VDC. No significant increase in tumors was observed in CD, Wistar, and Sprague–Dawley rats exposed to VDC by inhalation for 12, 12, and 18 months, respectively (Lee *et al*., 1978; Viola and Caputo, 1977; Maltoni *et al*., 1977, 1985; Quast *et al*.,

1986). CD-1 mice exposed to VDC by inhalation for 6 or 12 months also showed no significant increase in tumors (Lee *et al.*, 1978; Hong *et al.*, 1981), and a study of VDC exposure in Chinese hamsters was negative (Maltoni *et al.*, 1977, 1985). An increase in tumor incidence was reported (Cotti *et al.*, 1988) for Sprague–Dawley rats exposed to VDC for 104 weeks, beginning *in utero*, but there is no indication whether the increase was statistically significant. An increase in kidney adenocarcinomas in male Swiss mice was observed following 12 months of VDC exposure (Maltoni *et al.*, 1977, 1985). Mammary carcinomas in female mice and pulmonary adenomas in both male and female mice were also increased, but the authors, noting the absence of a dose–response relationship and the appearance of these tumors in controls, did not attribute the mammary and pulmonary tumors to VDC. No dose-related, significant increases in tumors were observed in animals given VDC orally (Ponomarkov and Tomatis, 1980; Maltoni *et al.*, 1977, 1985; NTP, 1982; Quast, 1983).

There are several limitations to these studies. Only one of the inhalation studies involved exposure for an adequate duration (viz., Cotti *et al.*, 1988), but that study offered no statistical analysis of the data. All but one of the oral bioassays were of adequate exposure length, but none clearly demonstrated inclusion of a maximally tolerated dose (MTD). The studies by Maltoni and colleagues (Maltoni *et al.*, 1977, 1985; Cotti *et al.*, 1988) contain no description of their statistical analysis, making it impossible to determine whether appropriate tests or criteria for significance were used. Also, data from the "BT" set of experiments published on two separate occasions (Maltoni *et al.*, 1977, 1985) are not entirely consistent, and it is unclear which data are correct.

The only dose-related observation of a significant increase in tumors associated with VDC comes from one of these experiments in which kidney adenocarcinomas were increased in Swiss mice in one exposure group in one gender only. In another study using a similar, Swiss-origin mouse strain (CD-1) (Lee *et al.*, 1978), no increase in kidney tumors was observed in male or female mice with substantially greater VDC exposure (55 ppm, 6 h/day, 5 days per week versus 25 ppm, 4 h/day, 4–5 days per week; 52-week duration in both studies). This comparison suggests that an effect of VDC on kidney adenocarcinomas, if real, is species, strain, and gender specific. The strain specificity would exist not just in terms of Swiss mice, but to the particular substrain used in one laboratory. Normally, such findings are given limited weight in an assessment of human carcinogenic potential.

While the animal data are primarily negative, there is no animal study that does not possess at least one important weakness. Limitations of various studies in terms of exposure duration or doses (concentrations) tested, and in statistical analysis and presentation of data, lead to the conclusion that evidence from animal studies overall is inadequate.

Structural Analog Data

Many chlorinated compounds structurally related to VDC have been tested for carcinogenicity (Table 2). These studies indicate that the chlorinated ethane and ethylene compounds can have vastly different carcinogenic potentials, ranging from none to significant potential in animals. Unfortunately, there is no sound scientific basis to determine which of these might be more predictive of VDC than the others. That is, there is no basis to determine whether VDC is more like trichloroethylene, for example, which is carcinogenic in mice, or *cis-* or *trans*-1,2-dichloroethylene, which are not. Given the wide disparity in outcomes for the chlorinated ethylenes closest to VDC in chemical structure, and the absence of a mechanistic basis for selecting the most appropriate chemical analog (see "Mode of Action," below), comparisons with structurally related compounds offer no real insight into VDC carcinogenic potential.

The sole positive finding attributed to VDC in animal studies, male mouse renal adenocarcinomas, does not appear to be consistent with observations from other chlorinated ethanes and ethylenes. For some structurally similar chemicals (e.g., TCE and PCE) renal cancer has been observed in rats, but among mice, tumors in lung and liver represent the predominant significant findings (see, for example, TCE, PCE, chloroethane, 1,2-dichloroethane, and vinyl chloride in Table 2). If structural comparisons are able to contribute anything to the interpretation of VDC carcinogenicity data, it is that the mouse kidney would not be a site where tumors would be expected.

Mode of Action

The mode of action by which VDC might produce a carcinogenic response is unclear. Several studies indicate that VDC, with metabolic activation, is genotoxic *in vitro* in bacteria, yeast, and fungi (Bartsch *et al.*, 1975, 1979; Jones and Hathway, 1978; Bronzetti *et al.*, 1981; Oesch *et al.*, 1983; Roldan-Arjona *et al.*, 1991; Crebelli *et al.*, 1992), but the results of genotoxicity studies in mammalian cells (Drevon and Kuroki, 1979; Sawada *et al.*, 1987; McGregor *et al.*, 1991) have been equivocal. Among studies of genotoxicity *in vivo*, negative results were reported for dominant lethal mutations in mice and rats following oral administration of VDC (Anderson *et al.*, 1977; Short *et al.*, 1977). In mice given VDC orally, bone marrow cells were negative for micronuclei aberrations, and pregnant female mice given VDC intraperitoneally did not have any changes in fetal liver and blood micronuclei (Sawada *et al.*, 1987). A significant increase in point mutations and mitotic gene

TABLE 2
Tumorigenicity[a] of Various Chlorinated Ethanes and Ethenes

Compound	IARC—tumor sites	USEPA IRIS—tumor sites[b]
Chloroethane	Inhalation *Mice*—uterine carcinomas; hepatocellular tumors; alveolar/ bronchiolar tumors. *Rats*—skin tumors; glial-cell tumors (IARC, 1999).	Not available (IRIS, 2000).
Vinyl chloride	Oral and Inhalation *Mice, rats, hamsters*—mammary gland; lung; Zymbal gland; skin; liver angiosarcoma (IARC, 1987).	Angiosarcomas, hepatocellular carcinomas and neoplastic nodules (IRIS, 2000; USEPA, 2000).
1,2-Dichloroethane	Oral *Mice*—benign and malignant tumors of the lung; malignant lymphomas; hepatocellular carcinomas; mammary and uterine adenocarcinomas. *Rats*—forestomach carcinomas; benign and malignant mammary tumors; hemangiosarcomas.	Oral *Rats*—forestomach squamous cell carcinomas; circulatory system hemangiosarcomas; mammary adenocarcinoma. *Mice*—alveolar/bronchiolar adenomas; endometrial stromal polyps and sarcomas; hepatocellular carcinomas; mammary adenocarcinomas (IRIS, 2000).
	Inhalation *Mice*—hemangiosarcomas; bronchiolar–alveolar adenoma and carcinomas; mammary gland adenocarcinomas; endometrial stromal polyps. *Rats*—mammary tumors; subcuits fibromas; peritoneal mesotheliomas (IARC, 1999).	Topical treatment *Mice*—lung papillomas (IRIS, 2000).
1,1-Dichloroethane	—	Oral *Rats*—mammary gland adenocarcinomas and hemangiosarcomas (IRIS, 2000). *Mice*—hepatocellular carcinomas; benign uterine polyps (IRIS, 2000).
trans-1,2-Dichloroethylene	—	Substance has not undergone complete evaluation (IRIS, 2000).
cis-1,2-Dichloroethylene	—	Not classifiable as to human carcinogenicity (D) based on no data in humans or animals (IRIS, 2000).
1,1,1-Trichloroethane	Inadequate evidence (IARC, 1999).	Animal studies (one lifetime gavage in rats, one intermediate-term inhalation in rats) have not demonstrated carcinogenicity (IRIS, 2000).
1,1,2-Trichloroethane	Oral *Mice*—hepatocellular neoplasms; adrenal pheochromocytomas. *Rats*—no significant findings reported (IARC, 1991).	Oral *Mice*—hepatocellular carcinomas; pheochromocytomas (IRIS, 2000). *Rats*—no significant findings (IRIS, 2000).
Trichloroethylene	Oral *Rats*—renal cell tumors; interstitial-cell testicular tumors. *Mice*—benign and malignant liver tumors. Inhalation *Mice*—lymphoma; liver tumor; lung tumors. *Rats*—interstitial testicular tumors; renal-cell tumors. *Hamsters*—no increase in tumor incidence (IARC, 1995).	Withdrawn (IRIS, 2000).

TABLE 2—*Continued*

Compound	IARC—tumor sites	USEPA IRIS—tumor sites[b]
Tetrachloroethylene	Oral *Mice*—hepatocellular carcinomas. Inhalation *Mice*—hepatocellular adenomas and carcinomas. *Rats*—mononuclear-cell leukemia; nonsignificant increase in renal-cell adenomas and adenocarcinomas (IARC, 1995).	Not available at this time (IRIS, 2000).
1,1,1,2-Tetrachloroethane	Oral *Mice*—hepatocellular adenomas and carcinomas. *Rats*—negative results in males and inconclusive results in females (IARC, 1999).	Oral *Mice*—hepatocellular adenomas and carcinomas (IRIS, 2000). *Rats*—neoplastic liver nodules and carcinomas combined. NTP concluded that carcinogenicity was not demonstrated in rats, however (IRIS, 2000).
1,1,2,2-Tetrachloroethane	Oral *Mice*—hepatocellular carcinomas. *Rats*—no significant increase in tumors (IARC, 1999).	Oral *Mice*—hepatocellular carcinomas (IRIS, 2000). *Rats*—no significant findings (IRIS, 2000).

Note. —, no information available.

[a] Listing of tumor sites does not necessarily imply statistically significant findings.

[b] IRIS (2000). Printout of chemical: ethyl chloride (chloroethane), tetrachloroethylene, 1,1-dichloroethane, 1,1,2-trichloroethane, *trans*-1,2-dichloroethylene, trichloroethylene, 1,1,2,2-tetrachloroethane, 1,1,1-trichloroethane, *cis*-1,2-dichloroethylene, 1,2-dichloroethane, 1,1,1,2-tetrachloroethane, and 1,1-dichloroethylene.

conversion in the kidney and liver (but not lungs) was observed following VDC treatment by gavage in a host-mediated assay in Swiss mice (Bronzetti *et al*., 1981), and Reitz *et al*. (1980) observed dose-related DNA alkylation following VDC inhalation in mice and rats. However, the extent of DNA alkylation was low—orders of magnitude less than that produced by the genotoxic carcinogen dimethylnitrosamine included in the study as a positive control (Reitz *et al*., 1980). DNA repair was significantly increased only at 50 ppm VDC, above the concentration reported to produce a positive response in the study by Maltoni *et al*. (1977, 1985). These data suggest that if VDC possesses genotoxic activity *in vivo* at all, it is very weak.

Another common mode of carcinogenic action is through recurrent tissue injury. The VDC concentration associated with increased kidney tumors in the Maltoni *et al*. study (25 ppm) has been reported to produce extensive kidney injury in some studies (Short *et al*., 1977; Reitz *et al*., 1980) and was stated by Maltoni *et al*. (1977) to be the "highest dose bearable by Swiss mice for long-term exposure." If the male Swiss mouse kidney is particularly susceptible to repeated tissue injury with chronic VDC exposure, this could explain a species-, gender-, and perhaps even strain-specific tumorigenic response that currently exists in the VDC literature.

Two mechanisms have been proposed for VDC kidney toxicity. One possibility is that VDC intermediates formed from oxidative metabolism in the liver are conjugated with glutathione (GSH), and these GSH conjugates are transported in the blood to the kidneys (Ban *et al*., 1995). There, metabolism of the GSH conjugates by β-lyase in the kidney could produce electrophilic, cytotoxic products, although this has not been demonstrated for VDC. Also, among chemicals for which β-lyase activity is thought to be important in toxicity (e.g., trichloroethylene; Goeptar *et al*., 1995), rats are typically more sensitive to renal toxicity than mice, the opposite of what appears to be the case for VDC. The other mechanism involves kidney damage from the formation of cytotoxic VDC intermediates from CYP2E1 activity in the kidneys themselves. CYP2E1 in the kidneys is localized primarily in proximal tubular epithelial cells, where VDC damage preferentially occurs (Brittebo *et al*., 1993; Speerschneider and DeKant, 1995). CYP2E1 activity in the kidney correlates with VDC kidney damage, i.e., species, strain, and gender comparisons find that higher renal CYP2E1 activity is associated with greater nephrotoxicity from VDC (Speerschneider and DeKant, 1995). Further, experimental manipulation of CYP2E1 activity in kidneys by castration in male mice, or testosterone supplementation in females and castrated males, has been shown to produce corresponding changes in nephrotoxicity from VDC exposure (Speerschneider and DeKant, 1995).

These observations provide evidence for a relationship between CYP2E1 activity and renal toxicity, but not necessarily between renal toxicity and renal cancer. The CD-1 mouse, which had the highest renal CYP2E1 activity and susceptibility to renal toxicity in a comparison of mouse strains (Speerschneider and DeKant, 1995), did not develop excess renal (or other) tumors from VDC (Lee *et al*., 1978). Further, plausible demonstration of a recurrent tissue injury mode of action would require observation of significant renal pathology in the species, strain, and exposure group(s) with renal tumors and its absence, or at least significantly less pathology, in animals without tumors. Unfortunately, the descriptions of tissue pathology, other than the tumors themselves, are minimal in most of the existing studies, making such comparisons impossible. Thus, while a recurrent tissue injury mode of action is possible, information currently available to support this mode of action is ambiguous.

In the absence of a clear genotoxic effect *in vivo*, and without a coherent set of observations consistent with a mode of action involving recurrent tissue injury, there is as yet no established mechanistic basis for a carcinogenic effect of VDC. The existing mode of action data also offer no means to reconcile the observations of Maltoni *et al*. and Lee *et al*., i.e., why one study in a Swiss-derived mouse strain found a positive renal tumor response while another study using a similar mouse strain and higher exposures did not.

Totality of Evidence

Evidence from both human and animal studies is inadequate to assess the human carcinogenic potential of VDC. The only significant finding attributable to VDC in either animal or human studies is an increase in renal adenocarcinomas in male mice at one VDC concentration in one study. Based on comparison of tumorigenic responses to other chlorinated ethylenes in mice, kidney carcinogenicity would not be expected. Further, this tumor type was not increased in male (or female) mice of another closely related strain with higher VDC exposures, nor in studies of male or female rats and Chinese hamsters. It is possible that the positive finding in one study is due to a species-, strain-, and gender-specific carcinogenic response to VDC, but the absence of a confirmatory response in males of another Swiss-derived mouse strain make this more likely a contradictory finding.

The human and animal evidence for carcinogenicity are too weak to merit weight-of-evidence descriptors of either "carcinogenic in humans" or "likely to be carcinogenic in humans" in the narrative. Likewise, the data, although primarily negative, do not merit a descriptor of "not likely to be carcinogenic in humans," particularly since none of the inhalation studies involved lifetime exposures. A descriptor of "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" is potentially applicable, since it applies in situations where evidence is marginal or confined to a single positive study. However, given that the single positive study is contradicted by another of at least equal merit, and structural analogy, mode of action, and other key data offer no particular support for the positive finding, a descriptor of "data are inadequate for an assessment of human carcinogenic potential" would seem more appropriate.

CONCLUSIONS AND RECOMMENDATIONS

Both human and animal data currently available to assess potential VDC carcinogenicity are inadequate. Studies of VDC-exposed worker populations, while negative, are too small and have insufficient follow-up to draw any conclusions about VDC carcinogenicity in humans. Several studies have evaluated potential VDC carcinogenicity in laboratory animals after inhalation or oral exposure. While these studies are generally negative, most have important limitations. Only one study has reported significant increases in tumors attributed to VDC exposure, that of Maltoni and co-workers. Description of the experimental details of this study, including methods of statistical analysis, are poor, making the validity of this study open to question. Also, this finding was not confirmed in another study using a similar mouse strain and greater VDC exposures (Lee *et al*., 1978). Even if the positive findings of the Maltoni *et al*. study are accepted as valid, the apparent species, strain, and gender specificity of the response greatly limits its weight in implicating VDC as a carcinogen in humans. Using weight-of-evidence descriptors from the draft *Guidelines for Carcinogen Risk Assessment*, data currently available for VDC would appear most consistent with a descriptor in the narrative that "data are inadequate for an assessment of human carcinogenic potential."

The USEPA has developed an inhalation unit risk for VDC based on observations in mice from this study, and also a VDC oral cancer slope factor based on negative results in an NTP bioassay. Given the weakness of the underlying data, the use of these cancer potency values to estimate cancer risks is problematic. It is not only likely to be inaccurate, it implies a level of confidence in VDC human carcinogenicity that does not exist. Under the draft *Guidelines for Carcinogen Risk Assessment*, dose–response assessment would not be indicated for VDC. Without potency estimates from a dose–response assessment, quantitative estimates of cancer risk from VDC are inappropriate.

Greater clarity regarding the human carcinogenic potential of VDC could be gained from larger, more thorough studies of VDC-exposed workers, although it is probably not realistic to expect such studies to be conducted in the near future. At present, the best

indication that VDC might be carcinogenic comes from a study in Swiss mice. A study in this strain should be repeated using contemporary standards for conducting a rodent bioassay, including adequate exposure duration, an appropriate range of exposure concentrations, and accepted methods for statistical analysis of the data. The study should also include B6C3/F1 mice for comparison. Such a study could resolve whether tumorigenic responses from VDC in fact exist in Swiss mice, as well as provide a clearer basis to determine whether any responses are strain specific. If positive responses are found, follow-up mechanistic studies would be valuable in determining whether these responses are potentially relevant to humans.

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Exhibit G

PRINCIPLES OF TOXICOLOGY

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PRINCIPLES OF TOXICOLOGY

Environmental and Industrial Applications

SECOND EDITION

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CONTENTS

TABLE 13.13 Agents Listed in the *Report on Carcinogens* (8th Edition) from the National Toxicology Program, as Known or Suspected Human Carcinogens

Known Human Carcinogens	
Aminobiphenyl (4-aminodiphenyl)	Erionite
Analgesic mixtures containing phenacetin	Lead chromate
Arsenic compounds, inorganic	Melphalan
Asbestos	Methoxsalen [with ultraviolet A (UVA) therapy]
Azathioprine	Mineral oils
Benzene	Mustard gas
Benzidine	2-Naphthylamine (β-naphthylamine)
Bis(chloromethyl) ether	Piperazine Estrone Sulfate
1,4-Butanediol dimethylsulfonate (Myleran)	Radon
Chlorambucil	Sodium equilin sulfate
1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea	Sodium estrone sulfate
	Soots
Chloromethyl methyl ether	Strontium chromate
Chromium hexavalent	Tars
Coal tar	Thiotepa [tris(1-aziridinyl)phosphine sulfide]
Coke oven emissions	Thorium dioxide
Creosote (coal)	Tris(1-aziridinyl)phosphine sulfide (thiotepa)
Creosote (wood)	Vinyl chloride
Cyclophosphamide	Zinc chromate
Cyclosporin A (cyclosporine A; ciclosporin)	
Diethylstilbestrol	
Agents Reasonably Anticipated to be Human Carcinogens	
Acetaldehyde	Beryllium zinc silicate
2-Acetylaminofluorene	Beryl ore
Acrylamide	Bis(chloroethyl) nitrosourea (BCNU)
Acrylonitrile	Bis(dimethylamino)benzophenone
Adriamycin (doxorubicin hydrochloride)	Bromodichloromethane
2-Aminoanthraquinone	1,3-Butadiene
o-Aminoazotoluene	Butylated hydroxyanisole (BHA)
1-Amino-2-methylanthraquinone	Cadmium
Amitrole	Cadmium chloride
o-Anisidine hydrochloride	Cadmium oxide
Azacitidine (5-azacytidine)	Cadmium sulfate
Benz[*a*]anthracene	Cadmium sulfide
Benzo[*b*]fluoranthene	Carbon tetrachloride
Benzo[*j*]fluoranthene	Ceramic fibers
Benzo[*k*]fluoranthene	Chlorendic acid
Benzo[*a*]pyrene	Chlorinated paraffins (C12, 60% chlorine)
Benzotrichloride	1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)
Beryllium aluminum alloy	Chloroform
Beryllium chloride	3-Chloro-2-methylpropene
Beryllium fluoride	4-Chloro-*o*-phenylenediamine
Beryllium hydroxide	*p*-Chloro-*o*-toluidine
Beryllium oxide	*p*-Chloro-*o*-toluidine hydrochloride
Beryllium phosphate	Chlorozotocin
Beryllium sulfate tetrahydrate	

(*continued*)

TABLE 13.13 Continued

CI[a] Basic Red 9 monohydrochloride	Ethyl acrylate
Cisplatin	Ethylene oxide
p-Cresidine	Ethylene thiourea
Cristobalite [under "Silica, crystalline (respirable size)"]	Ethyl methanesulfonate
	Formaldehyde (gas)
Cupferron	Furan
Dacarbazine	Glasswool
2,4-Diaminoanisole sulfate	Glycidol hexachlorobenzene
2,4-Diaminotoluene	α-Hexachlorocyclohexane
Dibenz[*a,h*]acridine	β-Hexachlorocyclohexane
Dibenz[*a,j*]acridine	γ-Hexachlorocyclohexane
Dibenz[*a,h*]anthracene	Hexachlorocyclohexane
7*H*-Dibenzo[*c,g*]carbazole	Hexachloroethane
Dibenzo[*a,e*]pyrene	Hexamethylphosphoramide
Dibenzo[*a,h*]pyrene	Hydrazine
Dibenzo[*a,i*]pyrene	Hydrazine sulfate
Dibenzo[*a,l*]pyrene	Hydrazobenzene
1,2-Dibromo-3-chloropropane	Indeno[1,2,3-*cd*]pyrene
1,2-Dibromoethane [ethylene dibromide (EDB)]	Iron dextran complex
1,4-Dichlorobenzene (*p*-dichlorobenzene)	Kepone (chlordecone)
3,3-Dichlorobenzidine	Lead acetate
3,3-Dichlorobenzidine dihydrochloride	Lead phosphate
Dichlorodiphenyltrichloroethane (DDT)	Lindane
1,2-Dichloroethane (ethylene dichloride)	Mestranol
1,3-Dichloropropene (technical-grade)	2-Methylaziridine (propylenimine)
Diepoxybutane	5-Methylchrysene
N,N-Diethyldithiocarbamic acid 2-chloroallyl esterDEHP; bis(2-ethylhexyl phthalate)]	4,4-Methylenebis(2-chloraniline)
	4,4-Methylenebis(*N,N*-dimethylbenzenamine)
Diethylnitrosamine	Methylene chloride
Diethyl sulfate	4,4-Methylenedianiline
Diglycidyl resorcinol ether	4,4-Methylenedianiline dihydrochloride
1,8-Dihydroxyanthraquinone [Danthron]	Methylmethanesulfonate
3,3-Dimethoxybenzidine	*N*-Methyl-*N*-nitro-*N*-nitrosoguanidine
4-Dimethylaminoazobenzene	Metronidazole
3,3-Dimethylbenzidine	Mirex
Dimethylcarbamoyl chloride	Nickel
1,1-Dimethylhydrazine (UDMH)	Nickel acetate
Dimethylnitrosamine	Nickel carbonate
Dimethyl sulfate	Nickel carbonyl
Dimethylvinyl chloride	Nickel hydroxide
1,6-Dinitropyrene	Nickel hydroxide
1,8-Dinitropyrene	Nickelocene
1,4-Dioxane	Nickel oxide
Direct Black 38	Nickel subsulfide
Direct Blue 6	Nitrilotriacetic acid
Disperse Blue 1	*o*-Nitroanisole
Epichlorohydrin	6-Nitrochrysene
Estradiol-17b	Nitrofen
Estrone	Nitrogen mustard hydrochloride
Ethinylestradiol	2-Nitropropane

(*continued*)

TABLE 13.13 Continued

1-Nitropyrene	1,3-Propane sultone
4-Nitropyrene	β-propiolactone
N-Nitroso-*n*-butyl-*N*-(3-carboxypropyl)amine	Propylene oxide
N-Nitroso-*n*-butyl-*N*-(4-hydroxybutyl)amine	Propylthiouracil
N-Nitrosodi-*n*-butylamine	Quartz [under "silica, crystalline (respirable size)"]
N-Nitrosodiethanolamine	Reserpine
N-Nitrosodi-*n*-propylamine	Saccharin
N-Nitroso-*N*-ethylurea (*N*-ethyl-*N*-nitrosourea (ENU)	Safrole
4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone	Selenium sulfide
N-Nitroso-*N*-methylurea	Silica, crystalline (respirable size)
N-Nitrosomethylvinylamine	Streptozotocin
N-Nitrosomorpholine	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)
N-Nitrosonornicotine	Tetrachloroethylene (perchloroethylene)
N-Nitrosopiperidine	Tetranitromethane
N-Nitrosopyrrolidine	Thioacetamide
N-Nitrososarcosine	Thiourea
Norethisterone	Toluene diisocyanate
Ochratoxin A	*o*-Toluidine
4,4-Oxydianiline	*o*-Toluidine hydrochloride
Oxymetholone	Toxaphene
Phenacetin	2,4,6-Trichlorophenol
Phenazopyridine hydrochloride	1,2,3-Trichloropropane
Phenoxybenzamine hydrochloride	Tridymite
Phenytoin	Tris(2,3-dibromopropyl) phosphate
Polybrominated biphenyls (PBBs)	Urethane (Urethan; ethyl carbamate)
Polychlorinated biphenyls (PCBs)	4-Vinyl-1-cyclohexene diepoxide
Polycyclic aromatic hydrocarbons (PAHs)	
Procarbazine hydrochloride	
Progesterone	

[a]Color Index.

was a "cancer epidemic" in this nation attributable to environmental exposure to pollutants shown to cause cancer in animals has been found to be inaccurate. In the absence of large percentages of cancers attributable to environmental contaminants or occupational exposures, then, we are faced with determining how much of our cancer risk is inevitable (due to aging processes or perhaps genetic predisposition) or could be offset by changes to lifestyle factors such as smoking and diet.

Genetic Makeup of Individuals

The understanding of the role that genetics plays in carcinogenesis increased greatly in the 1990s and the relationship between genetic makeup and carcinogenesis is rapidly becoming a dominant area of cancer research. To date there have been more than 600 genetic traits associated with an increased risk of neoplasia. This relatively recent area of research is focused on how changes in the phenotypic expression of certain enzymes may alter the activation, detoxification, or repair mechanisms and thereby enhance the genetic damage produced by a particular chemical exposure. Genetic predisposition now accounts for perhaps 5–10 percent of all cancers, and it has been identified as a component

Exhibit H

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Comments on recent discussions providing differing causation methodologies

RC James[1], J Britt[1], NC Halmes[2] and PS Guzelian[3]

Recently, we and others have proposed the methods of mapping the widely accepted logic underlying evidence-based medicine (EBM) in the field of toxicology.[1–5] The goal of evidence-based toxicology (EBT) is to provide a consistent, objective, and rule-based methodology for evaluating human and animal toxicology data to determine whether a chemical creates a human health risk; that is, whether the chemical is known to cause a specific toxic or adverse health effect in humans.[1,6,7] Early adopters of EBT include scientists and regulatory groups such as the U.S. Food and Drug Administration and the National Academy of Sciences critique of the U.S. Environmental Protection Agency (USEPA).[8–11] EBT is being evaluated by the USEPA itself at a recent workshop with some evident initial confusion. A report by some presenters[12] miscites the order and contents of originating EBT publications, incorrectly suggests that the systematic reviews are somehow equivalent to EBT rather than just one fundamental step in the process, and would have EBT focus on nonhuman animal studies to the virtual exclusion of human effects. Remarkably, the word "cause" or "causation" does not appear in the article, even though Hartung, a basic toxicologist initiator of EBT, considers causation of human health effects as one of the four pillars of the "temple" of EBT.[5]

Recently, two publications discussed alternative, but contradictory, approaches for analyzing animal and human data when trying to reach cause and effect conclusions.[13,14] Here, we discuss some shortcomings of these two contrasting proposals viewed from a perspective of a comprehensive framework for causation, that is, EBT.[1]

The proposed Epid-Tox framework

Adami et al.[13] proposed a causation framework they called Epid-Tox that adopted some of the strengths of EBM/EBT[1] and endorsed, at least in part, consideration of the widely accepted causation criteria originally published and discussed by Sir Austin Bradford Hill.[15] We agree that incorporating a set of checkpoints or criteria established ex ante into an evidence-based approach reduces the potential for biased conclusions and provides a basis for discovering what the Institute of Medicine (IOM)[14] referred to as a "more definitive algorithm for recognizing causality" in the future. However, Adami et al.[13] also proposed a pivotal role for animal toxicology data in the Epid-Tox approach. Given the well-known limitations of the predictive value of animal studies for human toxicity,[16,17] we question the fungibility of larger number of animal experiments as replacement data when the human studies are insufficient to determine causation.

The Epid-Tox framework correctly acknowledges that when there are insufficient animal data (y-axis) and insufficient human data (x-axis; see their Figure 4, the grey-shaded area covering the spot where the x- and y-axes cross), causation is an area of *uncertainty*. However, their Figure 4 also suggests that limitations in the human data can be overcome simply by developing more animal data (see x-axis above grey shading in Figure 4). (We believe the grey shading should extend from the top to the bottom of the figure along the x-axis, where human data are either absent or insufficient to assess the human outcome.) So, in the Epid-Tox process, the accretion of animal data overcomes insufficient human data and is shown as changing the opinion from unknown/uncertain to "likely causal" or "unlikely causal" (follow the y-axis up and down past the grey-shaded area representing *uncertainty*). In addition, a conclusion of "likely" or "unlikely" regarding any hypothesized human cause and effect relationship can be reached without sufficient,

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informative epidemiology. But Adami et al.[13] offer no empirical evidence to demonstrate that animal data are necessarily a substitute for required human evidence. As but one counterfactual example, the pharmaceutical industry routinely collects robust multidose, multispecies, acute, and chronic data in animals, only to find in subsequent human experiments that their candidate drugs are ineffective or cause unexpected human toxicities (e.g. two classic examples of the latter problem include thalidomide and hormone replacement therapy). The proposed Epid-Tox scheme (see their Figure 4) also suggests sufficient positive human data are reduced to an "uncertainty" whenever the animal data are strongly negative, but the fallacy of this assumption was demonstrated decades ago with arsenic.

The proposed Epid-Tox framework fails to demarcate "sufficient" from "likely," and the latter designation can rest exclusively on evidence from animal studies. As such, clear human health hazards like cigarette smoking and arsenic would be assigned to the same category as is ascribed for chemicals for which the relevance of the animal evidence in human is not known. For decades, regulatory agencies like the USEPA have used animal data to identify the potential human health hazards and safe exposure guidelines for a given chemical exposure, where the goal is to protect human health.[1,15] But this is not equivalent to actually knowing human causation. The International Agency for Research on Cancer (IARC) and USEPA have long determined human causation based on human data of sufficient strength and consistency that are capable of confirming or denying the hazards suggested by animal studies. For this reason, the Epid-Tox's blurring of the distinction between those effects that possibly occur and those known to occur in humans seems to be an unnecessary step backward. In apparent agreement with our position, National Research Council's recent advice to USEPA was to abandon attempts to demonstrate causation where animal data are already present:

> . . . once the available evidence, either epidemiologic or experimental, is judged sufficient to establish that a given finding of toxicity or carcinogenicity is *potentially relevant* to humans, . . . the committee sees no reason for [USEPA] to spend time and resources to fine-tune the *hazard classification* . . .[18]

Of course, to avoid misunderstandings by the general public, communication of conclusions about a regulated hazard should acknowledge when such a characterization is policy-based and not evidence-based.

Because Adami et al.[13] do not demarcate between known human and suspect hazards, they have to categorize causation as "likely causal" and "unlikely causal." But terms such as "likely" or "probable" connote that there is a known probability for the truth value of the proposed "risk factor" (i.e. a known causal relationship), a notion we submit has not been shown to be valid empirically or mathematically.[1] Consistent with this problem, even the USEPA and IARC have recently adjured readers who, for decades, may have "misunderstood" that these agencies are only expressing a "qualitative" meaning when they use the terms "likely," "possibly," or "probably."[7]

Likewise, the Epid-Tox framework pushes for experimental design evaluations of all data but adopts a "weight-of-evidence" (WoE) assessment approach. This term, popular with regulatory agencies, sounds conscientious but is a term of art that may mean any level of rigorousness; it may mean as little as a literal counting of the number of positive versus negative papers or may mean as much as a structured or criteria-based method.[19] As Hartung[5] noted earlier in one of his discussions on EBT, analyzing the literature using a WoE approach is a highly subjective process derived from authoritative beliefs and as such carries with it uncertainty. Others have similarly argued that a WoE analysis is only useful for comparing and contrasting the data supporting competing causal hypotheses, but does not actually lead to a selection of the correct answer.[20,21] Adami et al.[13] themselves stated—*The data obtained in toxicological and epidemiological studies do not always lead to straightforward interpretation, and often different observers will differ in their conclusions*. This is the very problem inherent to the use of both WoE and authoritative analyses. In contrast, EBT is driven by a methodology where the quality of evidence for each study is derived from logical ranking and rating of system that allows "the evidence" to lead to a causation conclusion in a more rigorous and transparent analysis. Similarly, the Evidence-Based Toxicology Collaboration (e.g. see www.ebtox.com) may lead to better methods for analyzing toxicity data than that offered by a WoE approach. If it does, then the biologic plausibility of the animal data is strengthened, which may, in turn, improve the overall causation analysis.

Finally, by reducing causation to some unknown probability anchored by animal data that adopts "likely" in lieu of "possible versus known," Epid-Tox introduces the same uncertainty that is currently associated with regulatory risk assessments. This in turn means that the Epid-Tox, like regulatory risk

assessments before it, would no longer be useful for delineating the known causes of human disease.[22] This overemphasis of the supportive role toxicology plays in the causal analysis of the epidemiology data, either for purposes of expediency or some simplification of the process, is to abandon the very origin of causation (i.e. stating what human outcome is known to occur).

The IOM review and discussion

The recent IOM[14] evaluation of dioxin offers a discussion on the contributions of toxicology and epidemiology in causal evaluations that is essentially the opposite of the approaches proposed for in the Epid-Tox framework. The IOM panel pointed out the uncertainties associated with animal to man extrapolations that are inherent to toxicology test data and reiterated differences in physiology, the magnitude of dose tested, biology, and genetics as reasons why animal species will not always necessarily accurately predict the human hazard. Thus, IOM effectively disagreed with the Epid-Tox approach, which assumes animal data can be sufficiently conclusive by itself when human data are either absent or too limited to reach a causal conclusion. IOM emphasized that when animal data are discordant with sufficient epidemiology evidence, epidemiology wins.

Turning to the evaluation of epidemiologic evidence, Epid-Tox, like that proposed for EBT, first collects all the data and then applies a predefined system including the use of Hill criteria to judge the quality and amount of the epidemiologic data.[1,23] The goal is to avoid bias and produce a rigorous, transparent, and auditable causation conclusion. But IOM asserts that there is no objective means for knowing causation, and the best that can be offered is consensus opinion built by individual committee member evaluation. IOM argued that causation decisions cannot be accomplished by a rule-based method. IOM could not seem to find a "definitive set of factors" and intoned that philosophers have proven that none exists. Indeed, in an ultimate embrace of skepticism, IOM states that, actually, there is no causation: *The establishment of causality is not an absolute or discrete (or necessarily permanent) state.* Philosophic debate aside, science regularly establishes some categorical and final causal truths: contact lenses cause visual acuity to improve, hitting one's thumb with a hammer can cause pain, and Galileo's hypothesis that the cause for the sun's rise each day is the heliocentric model of the solar system are known to be correct. However, even if IOM is correct, then the best they can offer us is just another opinion. In toxicology,[1] as in other fields,[24] authoritative opinions offered by "experts" can be demonstrated to be no more likely correct than that of nonexperts. Indeed, "expert" opinion has been a known problem in the field of toxicology: different scientific groups using self-selected, unsystematic methods as is advocated by IOM have been demonstrated to be biased in their data selection, data interpretation, and data evaluation and reach different causation conclusions sometimes from the same database.[1,15,25,26] In reversion to an unstructured authoritarian process, IOM[14] essentially condemns toxicology to the realm of a social science, where causation can seldom be proven, or as they suggest never is proven. In contrast, use of EBT reduces variation in authoritative consensus opinions, and where differences arise, the underlying reason/reasons can be spotted and evaluated. This issue and its ramifications has been discussed in some detail elsewhere.[1]

For more than a century, medicine made causal conclusions about diagnosis, treatment, prevention, or causation through the expressed wisdom of authoritative experts. Within the last two to three decades, medicine supplanted this approach *by the conscientious, explicit and judicious use of the best evidence as determined from a systematic, objective, and unbiased review of accumulated human knowledge*.[1] EBM/evidence-based logic (EBL) provides an objective, unbiased, and rigorous approach for making causation conclusions, is required material for all medical students seeking to pass the standardized national examination,[27] and has been extolled as *one of the top 15 milestones achieved in medicine*.[28] We have proposed a comprehensive framework for application of the same EBL to questions of causation in the field of human toxicology. The process of accepting new advances in causal reasoning in the field of toxicology has not unexpectedly experienced some resistance, as illustrated recently by two divergent frameworks, the IOM and Epid-Tox approaches. Notably, they offer mutually inconsistent approaches and neither has been empirically validated. For toxicologists seeking to determine what harms chemicals may cause in humans when sufficient epidemiological evidence is available, EBT offers a contemporary and recognized way to reach objective, unbiased, reproducible, and transparent causation conclusions. Its framework offers the same EBL methodology that continues to be the only acceptable causation methodology in medicine and many other scientific disciplines.[1]

Authors' Note

The authors have consulted or testified for parties involved in regulatory and litigation issues where the toxicities caused by chemical exposures were at issue.

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Exhibit I

FAST TRACK

Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study

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ABSTRACT

OBJECTIVE
To perform an expedited assessment of cancer risk associated with exposure to N-nitrosodimethylamine (NDMA) through contaminated valsartan products.

DESIGN
Nationwide cohort study.

SETTING
Danish health registries on individual level prescription drug use, cancer occurrence, and hospital diagnoses.

PARTICIPANTS
5150 Danish patients with no history of cancer, aged 40 years or older, and using valsartan at 1 January 2012 or initiating use between 1 January 2012 and 30 June 2017. Participants were followed from one year after cohort entry (lag time period) until experiencing a cancer outcome, death, migration, or end of study period (30 June 2018). Each participant's exposure to NDMA (ever exposure and predefined categories of cumulative valsartan exposure) was mapped out as a time varying variable while also applying a one year lag.

MAIN OUTCOME MEASURES
Association between NDMA exposure and a primary composite endpoint comprising all cancers except non-melanoma skin cancer, estimated using Cox regression. In supplementary analyses, the risk of individual cancers was determined.

RESULTS
The final cohort comprised 5150 people followed for a median of 4.6 years. In total, 3625 cohort participants contributed 7344 person years classified as unexposed to NDMA, and 3450 participants contributed 11 920 person years classified as ever exposed to NDMA. With 104 cancer outcomes among NDMA unexposed participants and 198 among exposed participants, the adjusted hazard ratio for overall cancer was 1.09 (95% confidence interval 0.85 to 1.41), with no evidence of a dose-response relation (P=0.70). For single cancer outcomes, increases in risk were observed for colorectal cancer (hazard ratio 1.46, 95% confidence interval 0.79 to 2.73) and for uterine cancer (1.81, 0.55 to 5.90), although with wide confidence intervals that included the null.

CONCLUSIONS
The results do not imply a markedly increased short term overall risk of cancer in users of valsartan contaminated with NDMA. However, uncertainty persists about single cancer outcomes, and studies with longer follow-up are needed to assess long term cancer risk.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Some valsartan products are suspected of having been contaminated with N-nitrosodimethylamine (NDMA), which is classified as carcinogenic to humans

After the discovery, European medical agencies and the US Food and Drug Administration withdrew affected valsartan products from the market

WHAT THIS STUDY ADDS

Among Danish valsartan users, exposure to NDMA contaminated valsartan was not associated with a markedly increased risk of overall cancer (adjusted hazard ratio 1.09, 95% confidence interval 0.85 to 1.41)

Future studies are, however, required to evaluate the risks for single cancer outcomes as well as long term effects

Introduction

Valsartan is an angiotensin II receptor antagonist used to treat hypertension and heart failure.[1 2] In July 2018, some valsartan products were discovered to have been contaminated with N-nitrosodimethylamine (NDMA).[3] This contamination, which far exceeded regulatory exposure limits, was specific to drug products manufactured by Zhejiang Huahai Pharmaceuticals, a company in Linhai, China, and seems to be related to a change in the manufacturing process that was implemented in 2012. Consequently, medical agencies across Europe as well as the US Food and Drug Administration have withdrawn all affected valsartan products from the market as of July 2018.[3]

NDMA is the simplest dialkylnitrosamine and is known to be a by-product in various industries—for example, the manufacture of pesticides, rubber tyres, alkylamines, and dyes.[4] NDMA is one of the most well characterised and most potent animal carcinogens known and has been shown to be a potent carcinogen across all species that have been investigated, both as single doses and with long term exposure to lower quantities.[5] Although no in vivo data are available for humans, NDMA seems to be metabolised similarly in human tissue and rodent tissue.[6] The International Agency for Research on Cancer (IARC) has on this basis classified NDMA as "probably carcinogenic to humans" (group 2A), emphasising that NDMA "should be regarded for practical purposes as if it were carcinogenic to humans."[7]

We accessed the nationwide Danish healthcare registries and conducted an expedited observational cohort study of the association between use of potentially NDMA contaminated valsartan products and risk of cancer. Our aim was to quantify the potential consequences of NDMA contaminated drug products entering the market and to provide timely information for regulatory bodies evaluating this potential public health issue.

Methods

We conducted a cohort study comparing cancer outcomes in users of potentially NDMA contaminated valsartan products with users of valsartan products assumed free from this contaminant.

Data sources and linkage

We obtained data from four Danish nationwide registries: the Danish Cancer Registry,[8 9] the National Prescription Registry,[10] the National Patient Register,[11] and the Civil Registration System.[12] Supplementary appendix A describes the data sources in detail and appendix B provides the codes for cancer diagnoses, drug exposures, and covariates. Data were linked by the personal identification number, a unique identifier assigned to all Danish residents since 1968.[13] Virtually all medical care in Denmark is provided by the national health authorities, allowing population based register linkage studies covering all legal residents of Denmark.

Study cohort

The study cohort comprised all Danish patients filling a valsartan prescription during the study period of 1 January 2012 to 30 June 2018. Prevalent users of valsartan at the start of the study period—defined as individuals having filled a valsartan prescription in September to the end of December 2011, entered the study cohort at 1 January 2012, whereas incident users entered the study cohort at the day of filling their first valsartan prescription during the study period. As patients contributed risk time from one year after entering the study cohort, we excluded those with less than one year of follow-up, as they did not contribute to any of the analyses reported. For the same reason, we excluded incident users filling their first prescription after 30 June 2017. We further excluded patients with a record of a previous cancer except non-melanoma skin cancer; those with a recent migration before cohort entry (within two years) to ensure enough baseline data on all study participants; and those aged less than 40 years at cohort entry as both use of valsartan and cancer occurrence is rare among children and younger adults. Participants were followed until a cancer outcome, death, migration, or end of the study period (30 June 2018), whichever occurred first.

Ascertainment of NDMA exposure

Within the study cohort we mapped out each participant's exposure to NDMA contamination using the unique drug ID (Nordic article number) as recorded in the National Prescription Registry to identify the single valsartan product and its manufacturer. From the 128 unique valsartan drug products used during 2012-18 within our study population, we identified 18 drug products (which constituted 18% of all prescriptions filled) that were manufactured using an active pharmaceutical ingredient from Zhejiang Huahai Pharmaceuticals. These drug products were classified as probably contaminated with NDMA. An additional 36 drug products (26% of all prescriptions) were classified as possibly contaminated with NDMA, as they contained an active pharmaceutical ingredient both from Zhejiang Huahai Pharmaceuticals and from other companies. Seventy four drug products (55% of all prescriptions) were classified as unlikely to be contaminated with NDMA as they did not contain an active pharmaceutical ingredient from Zhejiang Huahai Pharmaceuticals. In the main analysis we pooled together valsartan prescriptions classified as probably and possibly contaminated with NDMA, classifying those filling such prescriptions as ever exposed to NDMA from their first occurrence of such a prescription. We further stratified NDMA exposed person time by cumulative dose from filled prescriptions of potentially NDMA containing valsartan tablets (applying preplanned stratums of <20000, 20000-49999, and ≥50000 mg). The use of milligrams of valsartan as a scale for the dose-response analysis was based on the observation that the NDMA content for each tablet seems to correlate with the strength of the tablet.[14] With an estimated daily use of 80-160 mg (the defined daily dose of valsartan is 80 mg[15]), these cut-offs corresponded roughly to <200, 200-499, and ≥500 tablets. Of note, individuals classified as exposed to NDMA contributed follow-up to the non-exposed cohort until filling their first prescription for a potentially NDMA contaminated product. This ensured that the estimates were not affected by immortal time bias.[16]

Throughout all assessments of potential exposure to NDMA, we applied a one year lag time—that is, persons contributed NDMA exposed person time from one year after having filled their first prescription for a potentially NDMA containing valsartan product and onwards. This was done as very recent NDMA exposure (<1 year) is considered unlikely to materially affect an individual's risk of receiving a cancer diagnosis.[17] The length of the lag time was subjected to sensitivity analyses.

Cancer outcomes

We obtained cancer outcomes from the Danish Cancer Registry.[8 9] However, as data in this registry is currently only updated to 2016, we used the Danish National Patient Registry[11] to ascertain outcomes from 1 January 2017 to 30 June 2018. The primary outcome was a composite endpoint comprising all cancers (except non-melanoma skin cancer), as NDMA exposure is suspected to increase the risk of several different cancers. In supplementary analyses, we determined the risk of individual cancers, grouping cancers by organ system (ie, using codes from the international classification of diseases, 10th revision).

Covariates

The study cohort was described according to several characteristics that were also incorporated as covariates in the analyses: use of drugs (prescription fill <120 days before cohort entry) known or suspected to affect cancer risk, including low dose aspirin, non-aspirin non-steroidal anti-inflammatory drugs, 5-α reductase inhibitors, statins, spironolactone, oral

steroids, hormone replacement therapy, and selective serotonin reuptake inhibitors[18]; prior diagnoses (within five years from cohort entry) of diabetes, chronic obstructive pulmonary disease, heart failure, and alcohol related disease; Charlson comorbidity index scores (0, low; 1-2, medium; or ≥3, high; based on diagnoses established within the past five years before cohort entry)[19 20]; and whether the participant was a prevalent valsartan user at the beginning of the study period or initiated valsartan during the study period.

Main analysis
The primary analysis comprised a comparison of cancer occurrence during follow-up exposed to NDMA versus follow-up not exposed to NDMA. We used Cox regression to estimate the hazard ratio with 95% confidence intervals for cancer associated with NDMA exposure, both for ever use and for the predefined categories of cumulative use. The proportional hazards assumption was tested using Schoenfeld residuals. We carried out a formal dose-response test by categorising cumulative exposure to NDMA contaminated valsartan in categories of 10 000 mg as a time varying exposure and obtaining the P value for this variable as a continuous predictor of cancer risk in a Cox regression. As all comparisons were performed within users of valsartan, the exposure to NDMA can reasonably be expected to be a random event, and confounding is thus expected to be limited. Analyses were, however, performed as crude comparisons adjusted only for sex and age (age at cohort entry as continuous variable) as well as adjusted for sex, age, and the potential confounding factors. All analyses were performed using STATA Release 15.2.

Sensitivity and supplementary analyses
We carried out several sensitivity and supplementary analyses. Firstly, we performed analyses stratifying all participants by sex and age (40-69 and ≥70 years at cohort entry). Secondly, we restricted the cohort to prevalent valsartan users at the start of the study and to incident users during the study period. Thirdly, we restricted the ascertainment of NDMA exposure to prescriptions classified as probably contaminated with NDMA, while censoring individuals filling a prescription for a possibly NDMA contaminated drug product from the reference cohort (although allowing them to later enter the NDMA exposed cohort). Lastly, we varied the one year lag time period applied in the main analysis to six months and two years.

Patient and public involvement
No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing of results. There are no plans to disseminate the results of the research directly to the patient community. However, the results will be included in the ongoing review of the potential impact of NDMA contaminated valsartan on patients by the European Medicines Agency.

Results
In initial descriptive analyses, we identified 7068 unique individuals filling a total of 95 650 valsartan prescriptions from January 2012 to June 2018, the period where NDMA contaminated products were on the Danish market. The overall use of valsartan increased slightly during this period, in particular in 2017 and 2018 (fig 1), and the use of valsartan products possibly or probably contaminated with NDMA constituted about half of the total valsartan use, although this proportion dropped slightly during 2017-18.

For the selection of the study cohort, we identified 6406 individuals filling a valsartan prescription between September 2011 and June 2017. Of these, 5150 unique individuals met our inclusion criteria and entered the final cohort (fig 2), contributing a median of 4.6 years (interquartile range 2.0-5.5 years) of follow-up to the analysis, after the application of a one year lag period. Table 1 includes the baseline characteristics of valsartan users entering the study. A total of 3625 participants contributed 7344 person years of follow-up classified as unexposed to NDMA, and 3450 participants contributed 11 920 person years classified as ever exposed to NDMA (fig 2). The distribution of potentially NDMA contaminated and non-contaminated prescriptions were similar between the study cohort and all valsartan users (see supplementary figure 1).

Overall, exposure to potentially (probably or possibly) NDMA contaminated valsartan products showed no association with cancer compared with exposure to valsartan products unlikely to be contaminated with NDMA (adjusted hazard ratio 1.09, 95% confidence interval 0.85 to 1.41) and no evidence of a dose-response relation (P=0.70, table 2).

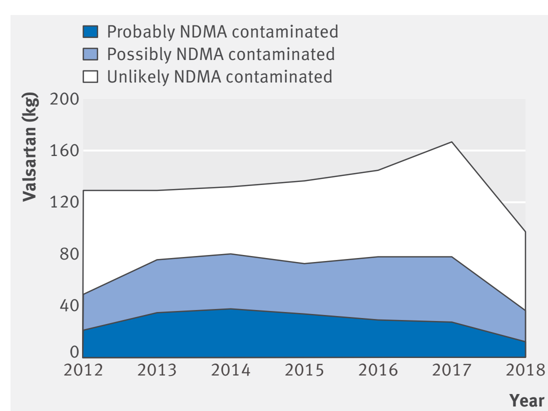

Fig 1 | Use of valsartan in kilograms of active substance, specified by drug products classified as probably, possibly, or unlikely to be contaminated with N-nitrosodimethylamine (NDMA). The drop in 2018 results from data only being available to June 2018

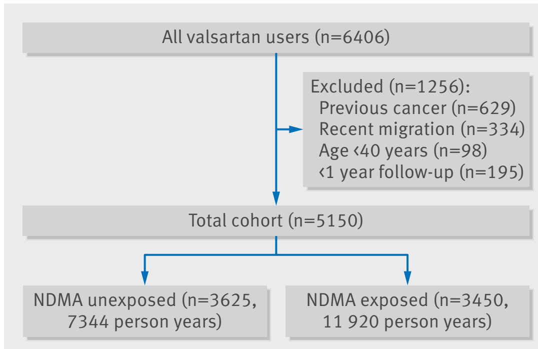

Fig 2 | Flowchart of cohort selection of Danish users of valsartan, January 2012 to June 2018. NDMA=N-nitrosodimethylamine

In analyses of single cancer outcomes, increased risks were seen for colorectal cancer (hazard ratio 1.46, 95% confidence interval 0.79 to 2.73) and for uterine cancer (1.81, 0.55 to 5.90), although neither these nor other single cancer outcomes reached statistical significance (fig 3). Analyses of other cancer outcomes were not possible owing to low numbers—that is, no cancer outcomes outside those included in figure 3 showed any associations with NDMA use.

Results comparable to the main analyses were found when we stratified by sex and age, whereas a stronger association was seen when we restricted to incident users during the study period (hazard ratio 1.58, 95% confidence interval 0.99 to 2.52) compared with prevalent users at the beginning of the study period (0.91, 0.66 to 1.25) (fig 4). A test for interaction between being an incident valsartan user and the effect of exposure to NDMA yielded a p value of 0.059.

The sensitivity analysis censoring individuals filling a prescription for a possibly NDMA contaminated valsartan product from the reference category yielded results comparable to those of the main analyses, both for overall cancer (see supplementary table 1) and for single cancers (see supplementary figure 2).

Varying the lag time from one year used in the main analyses to six months or two years yielded slightly higher risk estimates with increasing lag time, with the hazard ratio for ever exposure increasing to 1.17 (95% confidence interval 0.88 to 1.55) when a two year lag time was applied, although this did not reach statistical significance (see supplementary table 2).

Discussion

In this nationwide cohort study of Danish valsartan users, we did not see an increased short term overall risk of cancer associated with the use of valsartan products potentially contaminated with N-nitrosodimethylamine (NDMA).

Table 1 | Baseline characteristics of valsartan users entering study and among those potentially exposed and not exposed to N-nitrosodimethylamine (NDMA)

Characteristics	All (n=5150)	NDMA exposure	
		Exposed* (n=3450)	Not exposed* (n=3625)
Sex:			
Men	2531 (49.1)	1630 (46.9)	1745 (43.6)
Women	2619 (50.9)	1820 (53.1)	1880 (56.4)
Age (years):			
Median (interquartile range)	66 (58-74)	-	-
40-69	3195 (62.0)	2197 (65.0)	2164 (61.2)
≥70	1955 (38.0)	1253 (35.0)	1461 (38.8)
Prevalent valsartan users†:			
No	2870 (55.7)	2012 (51.2)	1353 (25.7)
Yes	2280 (44.3)	1438 (48.8)	2272 (74.3)
Charlson comorbidity score:			
0 (low)	3864 (75.0)	2697 (79.0)	2635 (74.9)
1	884 (17.2)	541 (15.3)	670 (17.1)
2	217 (4.2)	117 (3.2)	168 (4.5)
≥3 (high)	185 (3.6)	95 (2.5)	152 (3.4)
Drugs:			
Low dose aspirin	1388 (27.0)	842 (25.2)	1092 (29.2)
Non-aspirin NSAID	772 (15.0)	533 (15.5)	513 (16.0)
Statins	1924 (37.4)	1185 (35.1)	1457 (37.4)
Spironolactone	405 (7.9)	117 (3.2)	362 (4.9)
Glucocorticoids for systemic use	244 (4.7)	166 (4.5)	171 (4.3)
5-α reductase inhibitors	64 (1.2)	41 (1.2)	47 (0.9)
SSRIs	299 (5.8)	196 (5.7)	223 (6.0)
Hormone replacement therapy	454 (8.8)	319 (9.8)	338 (9.9)
Diagnoses:			
Diabetes type 1 and 2	899 (17.5)	559 (16.1)	667 (18.0)
Chronic obstructive pulmonary disease	247 (4.8)	131 (3.5)	200 (4.3)
Congestive heart failure	535 (10.4)	117 (2.9)	497 (5.3)
Alcohol related disease	48 (0.9)	28 (0.7)	34 (0.7)

NSAID=non-steroidal anti-inflammatory drug; SSRIs=selective serotonin reuptake inhibitors.
*Characteristics weighted by proportion of total time exposed or not exposed that individuals contributed, thereby providing the distribution of covariates in the main analysis comparison.
†Defined as being included in the study at 1 January 2012 by having filled a valsartan prescription between September and December 2011.

Table 2 | Estimates for association between use of valsartan products potentially contaminated with N-nitrosodimethylamine (NDMA) and cancer risk compared with non-contaminated valsartan products

NDMA exposure	Follow-up (person years)	Cancer outcomes	Incidence rate (/1000 person years)	Adjusted hazard ratio* (95% CI)	Fully adjusted hazard ratio† (95% CI)
Never use	7344	104	14.2	1.00 (ref)	1.00 (ref)
Ever exposure	11 920	198	16.6	1.16 (0.91 to 1.49)	1.09 (0.85 to 1.41)
Cumulative exposure (mg)‡:					
<20 000	3776	67	17.7	1.26 (0.92 to 1.72)	1.15 (0.83 to 1.59)
20000-49 999	2836	44	15.5	1.07 (0.75 to 1.53)	0.99 (0.69 to 1.43)
≥50 000	5308	87	16.4	1.14 (0.84 to 1.54)	1.11 (0.82 to 1.50)
Test for trend§				P=0.65	P=0.70

*Adjusted for age and sex.
†Adjusted for sex, age, use of low dose aspirin, non-aspirin non-steroidal anti-inflammatory drugs, 5-α reductase inhibitors, statins, spironolactone, oral steroids, hormone replacement therapy, or selective serotonin reuptake inhibitors, history of diabetes, chronic obstructive pulmonary disease, heart failure, or alcohol related disease, Charlson comorbidity index score, and being a prevalent valsartan user.
‡Defined by total amount of NDMA contaminated valsartan filled.
§Estimated using Cox regression across 10 000 mg stratums of NDMA contaminated valsartan filled.

Strengths and limitations of this study

The principal strength of this study is the use of high quality nationwide registries,[9 10 11] leaving little potential for selection bias.[12] Furthermore, the use of dispensing data, instead of data on prescribed drugs, as a proxy for NDMA exposure reduces the risk of misclassification due to primary non-adherence.[21] The principal weakness of the study is the limited median follow-up. Our findings only pertain to early cancer risk after exposure to NDMA whereas future studies are needed to elucidate the total cancer risk, which requires a substantially longer follow-up for the individual than what is currently available. Additionally, the limited follow-up combined with the low use of valsartan in Denmark leads to limited precision. Lastly, our exposure ascertainment is based on assumptions about NDMA content. Reassuringly, our sensitivity analysis disregarding less certain sources of NDMA returned estimates comparable to those of the main analysis. However, future studies should utilise data on the actual NDMA content of individual valsartan tablets once such information becomes available.

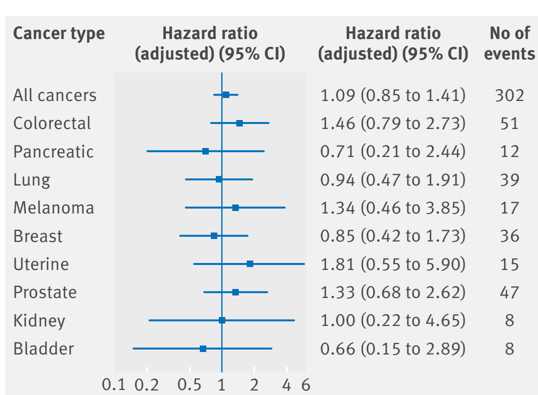

Fig 3 | Estimates for association between use of potentially N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of single cancer outcomes compared with users of non-contaminated valsartan products. Number of events are total number of events among valsartan users

Biological rationale

The International Agency for Research on Cancer (IARC) has classified NDMA as "probably carcinogenic to humans" owing to limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animal studies.[7] NDMA is suspected to have both localised and systemic carcinogenic effects due to the induction of DNA-damaging metabolites in the gastrointestinal tract and liver.[6 22] Specifically, in the liver, NDMA is metabolised by CYP2E1 to methyldiazonium, which causes mutations by methylation.[23] Also, N-nitroso compounds such as NDMA activate *ras* oncogenes, which are thought to play a role in the development of colon cancer.[6] As such, tumours in the gastrointestinal tract, lungs, kidneys, and liver have been seen in animal studies.[5 23 24] Evidence of carcinogenicity in rats was found at doses of about 10 µg/kg/day.[23] With concentrations of up to 22 µg NDMA in 320 mg valsartan tablets and 10 µg NDMA in 160 mg tablets,[14] the daily exposure for a 70 kg person ranges from 0.14 to 0.31 µg/kg/day. Even though it is not possible to extrapolate directly from animals to humans, the daily exposure in humans is thus roughly 30 times lower than the lowest dose leading to liver cancer in rats. Owing to the known carcinogenic effect of NDMA in animals,

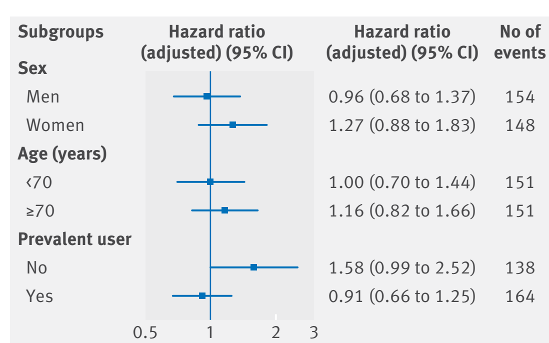

Fig 4 | Estimates for association between use of potentially N-nitrosodimethylamine (NDMA) contaminated valsartan products and cancer risk compared with users of non-contaminated valsartan products, specified by patient subgroups. Number of events are total number of events among valsartan users

no experimental studies in humans exist. However, as some dietary products (eg, processed meat) are known to contain small amounts of NDMA, epidemiological studies based on food frequency questionnaire data have been performed. Even though such studies are highly prone to confounding, three found an increased risk of gastrointestinal cancer with exposure to NDMA, predominantly colorectal cancer.[25 26 27] This finding, together with that from the animal studies, provides some support for the increased although statistically non-significant risk for this particular cancer observed in our study. Only one previous paper has reported on uterine cancer, finding no association between exposure to NDMA and uterine cancer in rats.[28] Lastly, no estimates could be obtained for liver cancer in our study owing to the absence of liver cancer events among those exposed to NDMA. A markedly increased risk of liver cancer associated with NDMA exposure thus seems unlikely.

Principal findings

Our estimates pertain to early cancer risk associated with exposure to NDMA through contaminated valsartan products and should not be interpreted as evidence against NDMA being carcinogenic to humans in general. At most, our findings suggest that the levels of NDMA exposure achieved through valsartan products do not translate into a substantially increased short term cancer risk. Furthermore, the fact that our study evaluates a potential safety concern holds some implications about how to interpret the results. While the estimate for our primary outcome suggests a negligible and statistically non-significant increase in cancer risk of 9%, it might be argued that a more cautious interpretation, reflecting the nature of the study question, would be to consider the upper limit of the confidence interval. Doing so leads to the different, although related, conclusion that we can reasonably exclude a more than 40% increased short term risk of cancer from exposure to NDMA contaminated valsartan products. A similar interpretation of the estimates obtained for the single cancer outcomes—in particular colorectal and uterine cancer—clearly highlights that our study cannot confidently rule out an increased risk from exposure to NDMA.

The finding that exposure to NDMA was associated with an increased risk of cancer specifically among users initiating valsartan treatment during the study period, as opposed to among valsartan users prevalent at the beginning of the study period, was a surprising finding that we cannot explain. The duration of follow-up was on average longer for prevalent users, as they were followed from the beginning of the study period (1 January 2012), and a late effect of exposure to NDMA therefore cannot explain this finding, as it would have led to an increased risk specifically among prevalent and not incident valsartan users. Considering the uncertainty about the actual NDMA content of valsartan products, it could be speculated that those using valsartan later in the study period might have been exposed to NDMA more often. However, no data are available that can be used to test this hypothesis. Lastly, our subgroup analyses had limited power and therefore the possibility of our results being a chance finding should also be considered.

Policy implications

Our findings can support regulators in their evaluation of the potential public health impact of exposure to NDMA through valsartan products. The Danish nationwide health registries and the strong research infrastructure hosted by Statistics Denmark and the Danish Health Data Authority, the latter of which was used in this study, gives researchers and regulators a unique possibility to provide answers to such emerging public health concerns in a timely manner. The present analysis was completed and submitted for publication within seven weeks after the finding of NDMA in valsartan products was announced publicly, and the paper published in *The BMJ* after a fast track peer review process spanning only three weeks from submission to publication. We previously performed a similar expedited assessment of a putative bleeding risk associated with use of generic warfarin,[29 30] although its publication was delayed by the peer review process for several months. Besides rapid peer review assessment, a close collaboration between researchers and regulators is a key element in ensuring both speed and relevance of such research projects. In addition to knowledge about the risks associated with exposure to NDMA, the present study provides proof-of-concept for such processes, which hold great promise for the use of pharmacoepidemiological input in the regulatory assessment of future public health crises.

Conclusion

We have assessed the potential cancer risk associated with exposure to NDMA through contaminated valsartan products and found no evidence of a markedly increased short term overall risk of cancer. However, we cannot exclude a modest association. Furthermore, owing to the limited follow-up, assessment of long term effects was not possible, and the low number of events makes interpretation of estimates for single cancer outcomes difficult. Therefore, further studies are needed to fully elucidate the health effects of NDMA contaminated valsartan products.

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Contributors: AP, JH, PQ, and NBJ conceived and designed the study. AP, KBK, and MTE performed the statistical analyses and data management. AP and KBK drafted the initial manuscript. All authors interpreted the data and revised the manuscript critically. AP is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: Statistical code is available from AP upon request. No additional data are available as Danish legislation does not allow disclosure of individual level data.

Transparency: The lead author (AP) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Supplementary information: appendices A and B

Exhibit J

Original Article

N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer

A Longitudinal Cohort Study Based on German Health Insurance Data

Willy Gomm, Christoph Röthlein, Katrin Schüssel, Gabriela Brückner, Helmut Schröder, Steffen Heß, Roland Frötschl, Karl Broich, Britta Haenisch

Summary

Background: N-Nitrosodimethylamine (NDMA), classified as a probable human carcinogen, has been found as a contaminant in the antihypertensive drug valsartan. Potentially carcinogenic effects associated with the consumption of NDMA-contaminated valsartan have not yet been analyzed in large-scale cohort studies. We therefore carried out the study reported here to explore the association between NDMA-contaminated valsartan and the risk of cancer.

Methods: This cohort study was based on longitudinal routine data obtained from a large German statutory health insurance provider serving approximately 25 million insurees. The cohort comprised patients who had filled a prescription for valsartan in the period 2012–2017. The endpoint was an incident diagnosis of cancer. Hazard ratios (HR) for cancer in general and for certain specific types of cancer were calculated by means of Cox regression models with time-dependent variables and adjustment for potential confounders.

Results: A total of 780 871 persons who had filled a prescription for valsartan between 2012 and 2017 were included in the study. There was no association between exposure to NDMA-contaminated valsartan and the overall risk of cancer. A statistically significant association was found, however, between exposure to NDMA-contaminated valsartan and hepatic cancer (adjusted HR 1.16; 95% confidence interval [1.03; 1.31]).

Conclusion: These findings suggest that the consumption of NDMA-contaminated valsartan is associated with a slightly increased risk of hepatic cancer; no association was found with the risk of cancer overall. Close observation of the potential long-term effects of NDMA-contaminated valsartan seems advisable.

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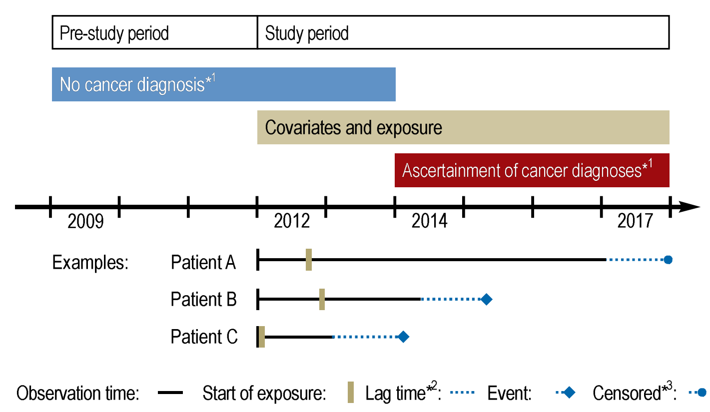
The angiotensin II receptor antagonist valsartan is used predominantly to treat hypertension and heart failure (1–4). In 2018, N-nitrosodimethylamine (NDMA) was detected in the valsartan active substance manufactured by Zhejiang Pharmaceuticals (5,6). Preparations containing the contaminated valsartan were withdrawn from the market by regulatory agencies across the world (5,7). In Germany, the Federal Institute for Drugs and Medical Devices (BfArM) ordered the recall of drug products contaminated with NDMA in July 2018. The NDMA contamination seems to be the result of a change in the manufacturing process in 2012 (8). Thus, patients may have been exposed to contaminated valsartan from 2012 until the recall. Investigations of other sartans with a tetrazole ring structure have revealed contamination with no more than small amounts of NDMA in only a few cases. NDMA is one of the most potent mutagenic carcinogens in animal models and was classified by the International Agency for Research on Cancer (IARC) as probably carcinogenic to humans (9–11).

A Danish cohort study based on healthcare system registry data reported no statistically significantly elevated overall risk of cancer and no increase in the risk of some individual cancers after exposure to drug products containing NDMA-contaminated valsartan (12). However, the sample size of the Danish study was limited to a total of 5150 patients, which may explain the non-significance of the results (12). For our cohort study we used a large longitudinal sample from the AOK, a large German statutory health insurance fund. We examined the association between filled prescriptions of potentially NDMA-contaminated valsartan drug product prescription and cancer risk in comparison with non-contaminated valsartan. Our results provide insights based on a substantially higher number of patients than in the Danish study. We also focus on various cancer outcomes with a large number of cancer events.

Methods

The *Figure* provides an overview of the study design. The data set comprises health insurance data from the AOK. It includes all patients aged 40 years or older at the beginning of 2012 who filled at least one prescription of valsartan between 1 January 2012 and 31

FIGURE



Overview of the study design

*1 For the evaluation of long-term use (3 years) the absence of cancer until the end of 2014 was required; follow-up started at the beginning of 2015.

*2 Depicted is the lag time of the main analysis (lag time of 1 year); for the evaluation of long-term use (3 years), no lag time was included.

*3 Data censored because of death, end of insurance cover, or end of study.

December 2017. Potential NDMA contamination was assessed on the basis of the pharmaceutical registration number (PZN) as product identifier in the filled prescription records and information on valsartan drug products from marketing authorization holders. The outcome was an incident cancer diagnosis. Cox regression models with time-varying variables and adjustment for potential influencing factors were used to calculate hazard ratios (HR) for cancer overall and for several individual cancer types. Detailed information can be found in the *eMethods*.

Results

The study cohort comprised 780 871 persons with a filled valsartan prescription during the period 2012–2017. Of these, 409 183 were classified as ever and 371 688 as never exposed to potentially NDMA-contaminated valsartan. The characteristics of the study cohort in 2012 are presented in *Table 1*. The mean and median person-times were 3.1 years (standard deviation 1.5 years) and 3.25 years (interquartile range 2–4.75), respectively.

For the outcome cancer overall, exposure to potentially NDMA-contaminated valsartan was not associated with an increased risk of an incident cancer diagnosis in comparison with exposure to non-contaminated valsartan (adjusted HR 1.00, 95% confidence interval [0.98; 1.02]; *eTable 1*). A similar result was obtained after adjustment for age and gender only (HR 1.01 [0.99; 1.03]). Based on the manufacturers' information about the packages of valsartan drug products sold, we were able to classify the filled valsartan prescriptions into different degrees of likelihood of contamination, from possibly to probably contaminated with NDMA *(eMethods)*. Exposure to neither possibly (adjusted HR 1.00 [0.97; 1.03]; *eTable 1*) nor probably (adjusted HR 0.99 [0.97; 1.02]; *eTable 1*) NDMA-contaminated valsartan was associated with the endpoint cancer overall. Differentiation between prevalent and incident exposure to potentially NDMA-contaminated valsartan showed no association with the endpoint cancer overall in either case (adjusted HR 0.97 [0.94; 1.01] and adjusted HR 1.01 [0.98 to 1.04], respectively; *eTable 1*). Higher exposure to potentially NDMA-contaminated valsartan, based on defined daily doses (DDDs), had no effect on the overall cancer rate *(eTable 1)*. For sensitivity analyses, the lag time between the last quarter assessed for exposure status and the initial cancer diagnosis or the end of the person-time was varied from 6 months to 2 years. We observed no significant differences across this lag time spectrum *(eTable 2)*. In a separate analysis we examined long-term use of valsartan, defined as filling of valsartan prescriptions in at least nine quarters of the first 3 years of the study period. Long-term use showed no association with the change in overall cancer rate (adjusted HR 0.96 [0.89; 1.04]); neither were dose-dependent effects observed *(eTable 1)*.

The analysis of individual cancer types showed a significant association between potentially NDMA-contaminated valsartan and liver cancer (adjusted HR 1.16 [1.03; 1.31], p = 0.017; *Table 2*). No association with potentially NDMA-contaminated valsartan exposure was detected for any other cancer outcomes *(Table 3)*. The association with liver cancer remained stable after basic adjustment for age and gender (HR 1.20 [1.06; 1.35]) and also after additional adjustment for hepatitis (ICD-10 codes B15–B19) and other liver diseases (ICD-10 codes K70–K76, Z944). Following correction for age and gender there was an increase from 34.6 to 39.1 per 100 000 person-years in the incidence rate of liver cancer for the valsartan-exposed population above 40 years of age according to the 2011 German census. However, no dose-dependent effect on the risk of liver cancer was found for higher exposure to potentially NDMA-contaminated valsartan *(Table 2)*. Varying lag times of 6 months to 2 years also did not alter the effect *(eTable 2)*. Evaluation of 3-year long-term use of potentially NDMA-contaminated valsartan resulted in a decreased sample size (75 112 patients, 130 cases of liver cancer) and showed no significant association with liver cancer (adjusted HR 1.22 [0.80; 1.89]; *Table 2*). The incidence rates for exposure and no exposure are given in *eTable 1* and *Table 2*.

Discussion

In our study we observed a slight elevation in the risk of liver cancer with the use of potentially NDMA-contaminated valsartan. Our analysis is based on a large longitudinal data set from a large statutory health insurance provider and on detailed information about potentially NDMA-contaminated valsartan from the marketing authorization holders of valsartan drug products.

Comparison with other studies on valsartan exposure

Only one cohort study on this topic has been published to date (12); the Danish registry study by Pottegard et al. has only a small sample size, comprising 5150 persons with prescription of valsartan. Our study contains around 150 times more persons with valsartan prescription. Pottegard et al. examined effects on the overall cancer rate and individual cancers, finding no statistically significant associations (HR for cancer overall 1.09 [0.85; 1.41] (12). However, the number of cancer cases in the Danish study was limited (302 cancers overall; only eight cases each of kidney and bladder cancer). The statistical power for detection of small effects is therefore limited, and no precise statements on small effect sizes can be made. With regard to qualitative effects, our findings are in agreement with the Danish study, as we detected no modification of cancer risk by potentially NDMA-contaminated valsartan for cancer overall or for the individual cancer types examined by the Danish authors.

For liver cancer, however, we observed a statistically significant association. This is interesting, as from a biological perspective liver cancer is the most likely form of cancer to resulting from NDMA contamination. That is the reason why we classified the occurrence of liver cancer as an independent primary endpoint compared with other specific types of cancer. Pottegard et al. did not report results for liver cancer, because no cases of liver cancer were detected among the persons who had received potentially NDMA-contaminated valsartan in the Danish study (12).

Strengths and limitations of the study

The main strength of our study is the cohort size of 780 871 persons with valsartan prescription and longitudinal health insurance claims data information from 2009 to 2017, drawn from the almost one third of the German population insured by the AOK (13, 14). This allowed us to perform analyses in an unselected patient population in a real-life setting, thus avoiding recall and selection bias. Another strength is that we received detailed information from the marketing authorization holders—e.g., which batches were produced with valsartan from Zhejiang Pharmaceuticals and how many packages were sold. These items of information are not included in the health insurance data. This enabled us to calculate the proportion of all batches with the relevant pharmaceutical registration numbers in Germany that contained potentially NDMA-contaminated valsartan.

The study also features limitations. Because the study is based on observational health insurance claims data (i.e., on non-randomized data), we cannot rule out residual confounding. Although we adjusted our analysis by including numerous potential influencing factors, some risk factors for cancer, such as smoking habits, nutritional habits, and genetic predisposition, are not available in routine health insurance data and, therefore, could not be integrated into the analysis. Nevertheless, the frequency of unmeasured cancer risk factors should be similar in the NDMA-exposed and non-exposed groups. However, we cannot rule out unmeasured confounders such as group differences in adherence patterns, due for instance to polypharmacy or differences in the Charlson comorbidity index. Inclusion of prevalent users did not alter the result. We detected only marginal differences between results with basic adjustment for age and gender and the fully adjusted model with all covariates. This indicates that the potentially influential factors included in the model had no strong effects. Although detailed batch-wise information on potentially NDMA-contaminated valsartan was provided, we had no information on the exact NDMA content of individual valsartan tablets. However, sensitivity analyses with varying degrees of possible or probable NDMA contamination yielded results comparable to those of the main analysis. A further limitation is that due to the limited follow-up time we were not able to monitor the long-term effects of

TABLE 1

Baseline characteristics of the study cohort

Characteristic		All (N = 780 871) (%)	NDMA exposure: Not exposed (n = 371 688) (%)	NDMA exposure: Exposed (n = 409 183) (%)
Gender	Male	312 146 (40.0)	156 360 (42.1)	155 786 (38.1)
	Female	468 725 (60.0)	215 328 (57.9)	253 397 (61.9)
Age: median (IQR)		68 (57–75)	66 (55–74)	69 (58–76)
Prevalent use	No	534 519 (68.5)	300 370 (80.8)	234 149 (57.2)
	Yes	246 352 (31.5)	71 318 (19.2)	175 034 (42.8)
SSRI		36 825 (4.7)	16 202 (4.4)	20 623 (5.0)
NSAID		316 350 (40.5)	150 730 (40.6)	165 620 (40.5)
5α-Reductase inhibitors		6136 (0.8)	2684 (0.7)	3452 (0.8)
Low-dose ASA		94 061 (12.0)	38 988 (10.5)	55 073 (13.5)
Statins		237 998 (30.5)	102 502 (27.6)	135 496 (33.1)
Spironolactone		25 235 (3.2)	9986 (2.7)	15 249 (3.7)
Glucocorticoids		72 493 (9.3)	32 805 (8.8)	39 688 (9.7)
Hormone replacement therapy		19 219 (2.5)	9025 (2.4)	10 194 (2.5)
Polypharmacy		456 508 (58.5)	197 710 (53.2)	258 798 (63.2)
Diabetes		277 266 (35.5)	125 388 (33.7)	151 878 (37.1)
COPD		103 474 (13.3)	45 356 (12.2)	58 118 (14.2)
Congestive heart failure		136 566 (17.5)	55 554 (14.9)	81 012 (19.8)
Alcohol-related disease		13 512 (1.7)	6665 (1.8)	6847 (1.7)
CCI	Low (0)	227 331 (29.1)	121 183 (32.6)	106 148 (25.9)
	Medium (1–2)	333 351 (42.7)	158 327 (42.6)	175 024 (42.8)
	High (≥ 3)	220 189 (28.2)	92 178 (24.8)	128 011 (31.3)

ASA, Acetylsalicylic acid; CCI, Charlson comorbidity index; COPD, chronic-obstructive pulmonary disease; IQR, interquartile range; NDMA, N-nitrosodimethylamine; NSAID, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitors

TABLE 2

Liver cancer risk due to use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan

	Hazard ratio [95% CI]*[1]	Sample size/ Cancer cases
Exposure to NDMA-contaminated valsartan		
No exposure	1.00 (ref)	354 628/444
Exposure	1.16 [1.03; 1.31]	385 167/736
Exposure in dose categories		
0 to ≤ 90 DDD	1.15 [0.98; 1.34]	122 479/244
> 90 to ≤ 170 DDD	1.19 [1.02; 1.40]	136 734/248
> 170 DDD	1.13 [0.97; 1.33]	125 954/244
NDMA exposure		
Possible (contaminated valsartan batches < 75%)	1.18 [1.01; 1.39]	104 433/232
Probable (contaminated valsartan batches ≥ 75%)	1.15 [1.01; 1.31]	280 734/504
Long-term valsartan use*[2]		
No exposure	1.00 (ref)	61 236/102
Exposure	1.22 [0.80; 1.89]	13 876/28
	Incidence rate per 100 000 person-years*[3]	
No exposure	34.61	
Exposure	39.08	

*[1] Lag time 1 year, fully adjusted for sex; age; polypharmacy (defined as prescription of five or more different drugs); prescription of low-dose acetylsalicylic acid (ASA), non-ASA non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors, statins, spironolactone, glucocorticoids for systemic use, selective serotonin reuptake inhibitors, and hormone replacement therapy; the comorbidities diabetes, chronic obstructive pulmonary disease, congestive heart failure, and alcohol-related diseases; the Charlson comorbidity index (score); and prevalent valsartan use

*[2] Long-term valsartan use is defined as valsartan prescription in at least nine quarters within the first 3 years of the study period.

*[3] Standardized to the German population over 40 years in 2011 (e2)

DDD, Defined daily dose; NDMA, N-nitrosodimethylamine; 95% CI, 95% confidence interval

NDMA-contaminated valsartan for more than 3 years.

Biological background

NDMA is classified by the IARC as probably carcinogenic (group 2A). It is carcinogenic in the tissues of experimental animal species with metabolism similar to that of human tissues (9, 15). Ingested NDMA is metabolized by cytochrome P450-dependent mixed-function oxidases to methyldiazonium ions, which alkylate proteins, DNA, and RNA (16–19). In experimental animals oral NDMA exposure increases tumor incidences in various organs, predominantly in the liver (19). Those effects become measurable at doses of about 10 µg/kg/day (19). In our study, exposure to NDMA elevated liver cancer risk independent of dose. This might support the hypothesis of a threshold dose for the development of cancer. NDMA can be found among other N-nitroso compounds in foods, especially those that are smoked or dried at high temperature (20). Epidemiological studies investigating the association between explicit dietary NDMA exposure and cancer yielded inconclusive results (21–23). No inferential statistical analyses were available on the association between human NDMA exposure and liver cancer. Nevertheless, exposure to NDMA-rich food in regions with high liver cancer rates in Thailand could potentially be based on a correlation, although no conclusive studies have been published (24). The observed rates of cancer overall and liver cancer in our study were around 1.5–2 times the national average. This is most likely due to the inclusion of persons aged 40 years and older for analysis, resulting in a study population older than the general population. The effect of NDMA exposure on liver cancer is a statistical result. However, molecular mechanisms known for NDMA in the pathogenesis of liver cancer in experimental animals support an association with NDMA exposure in humans. It may be that NDMA exposure promotes cancer development in already existing, as yet undiagnosed early stages and thus hastens clinical manifestation.

Regulatory and public health implications

Our study provides information for regulatory authorities worldwide to assess the public health impact of NDMA contamination in valsartan drug products. It is an example of how extensive real-world data from statutory health insurance funds can be used to examine urgent drug safety questions with pharmacoepidemiological methods. The immediate recall of all potentially NDMA-contaminated valsartan drug products by regulatory authorities worldwide was necessary in order to protect public health. The detection of different nitrosamine impurities in drug products since 2018 led to the introduction of a new threshold by the European Medicines Agency (25).

Conclusion

We examined the association of NDMA-contaminated valsartan drug products and cancer risk in a large health insurance data set including more than 780 000 persons. We detected a small, yet statistically significant increase in the risk for liver cancer with the use of NDMA-contaminated valsartan while no association was found for overall cancer risk or other examined single cancer outcomes. However, the present study can only state the existence of a statistical association. Causality cannot be inferred. Long-term effects of regular use of potentially NDMA-contaminated valsartan for more than 3 years could not be evaluated because of the currently still relatively short follow-up time. Therefore, careful monitoring of potential further effects of NDMA-contaminated valsartan after longer periods is advisable.

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Data sharing statement
The data cannot be shared with or transmitted to third parties due to legal restrictions.

Conflict of interest statement
The authors declare that no conflict of interest exists.

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TABLE 3

Risk of individual cancers owing to use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan

Exposure to NDMA-contaminated valsartan	Hazard ratio [95% CI]*1	Sample size/ Cancer outcomes
Outcome bladder cancer		
No exposure	1.00 (ref)	355 225/ 1041
Exposure	1.02 [0.95; 1.11]	385 922/ 1491
Outcome breast cancer		
No exposure	1.00 (ref)	208 262/ 1804
Exposure	1.02 [0.96; 1.08]	242 778/ 2736
Outcome colorectal cancer		
No exposure	1.00 (ref)	356 208/ 2024
Exposure	0.99 [0.94; 1.05]	387 297/ 2866
Outcome kidney cancer		
No exposure	1.00 (ref)	354 980/ 796
Exposure	0.96 [0.87; 1.05)	385 522/ 1091
Outcome lung cancer		
No exposure	1.00 (ref)	355 891/ 1707
Exposure	0.97 [0.91; 1.03]	386 710/ 2279
Outcome malignant melanoma		
No exposure	1.00 (ref)	354 934/ 750
Exposure	0.94 [0.85; 1.03]	385 414/ 983
Outcome pancreatic cancer		
No exposure	1.00 (ref)	354 897/ 713
Exposure	0.93 [0.84; 1.02]	385 398/ 967
Outcome prostate cancer		
No exposure	1.00 (ref)	149 514/ 1788
Exposure	1.00 [0.94; 1.06]	146 768/ 2379
Outcome uterine cancer		
No exposure	1.00 (ref)	206 944/ 486
Exposure	1.08 [0.96; 1.21]	240 801/ 759

*1 Lag time 1 year, fully adjusted for sex; age; polypharmacy (defined as prescription of five or more different drugs); prescription of low-dose acetylsalicylic acid (ASA), non-ASA non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors, statins, spironolactone, glucocorticoids for systemic use, selective serotonin reuptake inhibitors, and hormone replacement therapy; the comorbidities diabetes, chronic obstructive pulmonary disease, congestive heart failure, and alcohol-related diseases; the Charlson comorbidity index (score); and prevalent valsartan use

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► Supplementary material

eReferences, eMethods, eTables, eFigure:
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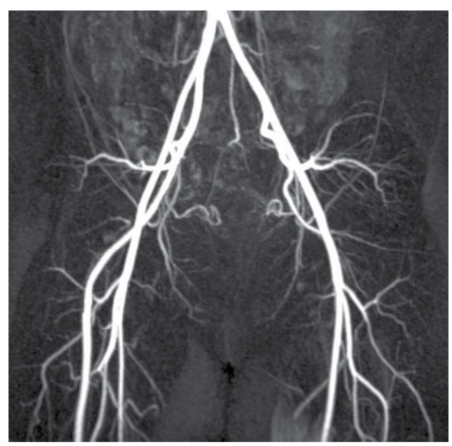
CLINICAL SNAPSHOT

A Rare Cause of Intermittent Claudication: Persistent Sciatic Artery

A 45-year-old female presented with claudication of the right lower extremity. Her ankle-brachial index (ABI) had dropped to 0.6. Angiography revealed an atypical course of the superior femoral artery without transitioning into the popliteal artery. The latter filled with contrast via collaterals in a delayed manner. We suspected a vascular anomaly. After probing the internal iliac artery, it was possible to pass a thrombotically occluded sciatic artery.
We initiated local thrombolysis with 1 mg rtPA/h for 20 h. Follow-up angiography showed decreased thrombus burden with underlying stenosis of the vessel. This was treated with a stent. Angiographic magnetic resonance imaging (MR angiography) 6 days following intervention revealed continuity of the schiatic artery *(Figure)*. Follow-up at 12 weeks showed normal ABI without reduced walking distance. Persistent sciatic artery is a rare anatomical variant that arises from the inferior iliac artery and normally regresses in favor of the femoral arteries. Due to poor vessel structure, the vessel is prone to vasculopathy.



MR angiography showing a right persistent sciatic artery.

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Supplementary material to:

N-Nitrosodimethylamine–Contaminated Valsartan and the Risk of Cancer

A Longitudinal Cohort Study Based on German Health Insurance Data

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eMETHODS

Sample and data source

The data set from the AOK includes information on age, gender, outpatient and inpatient diagnoses (coded using the International Classification of Diseases, 10th revision with German modification, ICD-10-GM) and filled drug prescriptions (categorized according to the Anatomical Therapeutic Chemical classification system ATC code) on a quarterly basis for the years 2009–2017. During the period 2009–2017, on average nearly 25 million persons were insured by the AOK each year.

Selection criteria and diagnoses

Patients were continuously insured by the AOK during the years 2009–2013. Any diagnosis of cancer (ICD C00 to C97, except C44) in the years 2009–2013 led to exclusion from analysis. This ensures that only incident cancer cases occurring in 2014 or later are detected, since the likelihood of recurrence of cancer after 5 years or more without an intervening cancer diagnosis is considered low.

New cancer diagnoses were considered valid if they were main or secondary hospital diagnoses or were documented in the outpatient sector as verified or "status post" diagnoses. For the outpatient diagnoses, at least one confirmatory diagnosis within the following four quarters was required for validation. For the analysis of selected cancer diagnoses (bladder, breast, colorectal, kidney, liver, lung, melanoma, pancreatic, prostate, and uterine cancer) the cancer type had to be the first valid cancer diagnosis. Diagnoses of other cancer types were present only in the index quarter itself or later. The index quarter was defined as the quarter with the first valid cancer diagnosis following the cancer-free period from 2009 to at least the end of 2013. Persons with other cancer diagnoses before the index quarter in which the examined cancer type was diagnosed were not included in the analysis for the specific individual cancer types. The *eFigure* provides an overview of the study cohort for evaluation after application of the selection and quality control criteria.

Exposure

The NDMA content of valsartan tablets seems to correlate with the dose strength of the tablet (e1). Therefore, the valsartan doses of the contaminated drug products can be used to categorize NDMA exposure.

All users had a filled prescription of valsartan within the observation period. The observation period concluded at the end of 2017 at the latest. Prevalent valsartan use was defined as a filled valsartan prescription in the first quarter of 2012. Incident use started at the time of the first filled prescription during the study period. Patients were considered as exposed from the first filled prescription until the end of the observation period.

The marketing authorization holders provided batch-related data on all valsartan drug products for the years 2012–2017. This included detailed information on which batches were manufactured using the active ingredient valsartan supplied by Zhejiang Pharmaceuticals and how many packages of these drug products were sold. Based on this information, we calculated the proportion of all packages of valsartan drug products sold made up by packages manufactured using contaminated ingredients. We calculated this ratio for all pharmaceutical registration numbers (PZN) affected by the recalls of valsartan drug products. We were thus able to divide the PZN into possibly contaminated (< 75% of sold packages with contaminated valsartan) and probably contaminated (≥ 75% of sold packages with contaminated valsartan). It was also possible to calculate the amount of the defined daily dose (DDD) of

contaminated valsartan drug products by multiplying the DDDs from the prescriptions with the previously calculated factors.

Because of the varying length of observation time, the use of cumulative doses may introduce bias. Therefore, we used dose categories and calculated the cumulative maximum of the dose as DDD in a given quarter within the observation time. The dose categories comprise the 33.3% and 66.6% percentiles of all non-zero maximum dose values. Dose categories were determined for the data set with a lag time of 1 year (four quarters) and were also used for sensitivity analyses. We calculated the DDD of contaminated valsartan by quarter and divided the patients into three equal groups with lowest, intermediate, or highest exposure based on the quarter of greatest exposure.

For the evaluation of long-term use of valsartan drug products, we used an exposure period of 3 years as baseline. Long-term use was defined as "patients with filled prescriptions in at least nine of the first twelve quarters (3 years) of the study period." Users of uncontaminated valsartan did not receive any prescriptions of possibly or probably contaminated valsartan in the first 3 years and were right-censored at the first quarter in which they received any contaminated valsartan. Thus, for users of uncontaminated valsartan, only time periods of uncontaminated valsartan use were included in the analysis. Users of possibly or probably contaminated valsartan were defined as having filled prescriptions of contaminated valsartan in at least nine of the twelve quarters. Additional use of uncontaminated valsartan was allowed.

Forty-seven percent of patients receiving potentially contaminated valsartan and 67% of patients receiving uncontaminated valsartan received their second prescription of valsartan with the same contamination status in the following quarter. Sixty-nine percent and 88% of patients, respectively, received a repeat prescription within 1 year after the initial prescription or dropped out of the study. Eighty percent of patients receiving contaminated valsartan and 93% of patients receiving uncontaminated valsartan received a second prescription with the same contamination status within 2 years after the initial dose or dropped out of the study.

Covariates

The following time-dependent covariates were included in the statistical analyses as potential influencing factors: age, gender, polypharmacy (defined as prescription of five or more different drugs), comedications that are known or suspected to affect cancer risk, such as low-dose acetylsalicylic acid (ASA), non-ASA non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors, statins, spironolactone, glucocorticoids for systemic use, selective serotonin reuptake inhibitors, and hormone replacement therapy. Furthermore, we included the following comorbidities as additional potential influencing factors: diabetes, chronic obstructive pulmonary disease, congestive heart failure, alcohol-related diseases, the Charlson comorbidity index (score), and presence of prevalent valsartan use at the beginning of the study period. Details of ATC and ICD-10 codes are given in *eTable 3*.

Statistical analyses

We applied Cox regression with time-dependent variables. We selected a lag time of 1 year, since short-term exposure is unlikely to modify the risk of cancer. For sensitivity analysis, we varied the lag time from 6 months to 2 years. In addition, there was a minimal observation time of 1 year before the lag time. For the evaluation of long-term use of valsartan drug products, patients with continuous valsartan prescription for at least 3 years were considered.

All calculations were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and were independently confirmed with R version

3.5.1. Any p-value < 0.05 (two tailed) was considered statistically significant. Hazard ratios (HR) are reported with 95% confidence intervals. Incidence rates were standardized using the 2011 German census for persons aged 40 years and over (e2).

eTABLE 1

Overall cancer risk from use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan

	Hazard ratio [95% CI]*1	Sample size/ cancer cases
Exposure to NDMA-contaminated valsartan		
No exposure	1.00 (ref)	371 688/17 504
Exposure	1.00 [0.98; 1.02]	409 183/24 752
Exposure in dose categories		
0 to ≤ 90 DDDs	1.00 [0.97; 1.03]	130 684/8449
> 90 to ≤ 170 DDDs	1.01 [0.99; 1.04]	144 876/8390
> 170 DDDs	0.98 [0.95; 1.00]	133 623/7913
NDMA exposure		
Possible NDMA exposure (contaminated valsartan batches <75%)	1.00 [0.97; 1.03]	111 962/7761
Probable NDMA exposure (contaminated valsartan batches >=75%)	0.99 [0.97; 1.02]	297 221/16 991
Only prevalent valsartan use*2		
No exposure	1.00 (ref)	71 318/5754
Exposure	0.97 [0.94; 1.01]	175 034/12 464
Only incident valsartan use*2		
No exposure	1.00 (ref)	300 370/11 750
Exposure	1.01 [0.98; 1.04]	234 149/12 288
Long-term valsartan use*3		
No exposure	1.00 (ref)	64 836/3472
Exposure	0.96 [0.89; 1.04]	14 686/817
Exposure in dose categories		
0 to ≤ 90 DDDs	1.00 [0.86; 1.17]	2629/166
> 90 to ≤ 170 DDDs	1.03 [0.89; 1.18]	3777/220
> 170 DDDs	0.91 [0.83; 1.01]	8280/431
	Incidence rate*4 per 100 000 persons	
No exposure	1254.71	
Exposure	1270.30	

*1 Lag time 1 year, fully adjusted for sex; age; polypharmacy (defined as prescription of five or more different drugs); prescription of low-dose acetylsalicylic acid (ASA), non-ASA non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors, statins, spironolactone, glucocorticoids for systemic use, selective serotonin reuptake inhibitors, and hormone replacement therapy; the comorbidities diabetes, chronic obstructive pulmonary disease, congestive heart failure, and alcohol-related diseases; the Charlson comorbidity index (score); and prevalent valsartan use
*2 Without covariate "prevalent valsartan use"
*3 Long-term valsartan use is defined as valsartan prescription in at least nine quarters within the first 3 years of the study period.
*4 Standardized to the German population over 40 years in 2011 (e2)
DDD, defined daily dose; NDMA, N-nitrosodimethylamine; 95% CI, 95% confidence interval

eTABLE 2

Overall cancer risk and liver cancer risk from use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan, different lag times

	Hazard ratio [95% CI]*	Sample size/ cancer cases
Cancer overall: valsartan prescription		
Lag time 6 months		
No exposure	1.00 (ref)	386 322/19 383
Exposure	1.00 [0.99; 1.02]	443 442/26 375
Lag time 12 months (main analysis)		
No exposure	1.00 (ref)	371 688/17 504
Exposure	1.00 [0.98; 1.02]	409 183/24 752
Lag time 24 months		
No exposure	1.00 (ref)	291 955/11 252
Exposure	0.99 [0.97; 1.01]	371 555/16 966
Liver cancer: valsartan prescription		
Lag time 6 months		
No exposure	1.00 (ref)	367 705/485
Exposure	1.16 [1.04; 1.31]	418 219/774
Lag time 12 months (main analysis)		
No exposure	1.00 (ref)	354 628/444
Exposure	1.16 [1.03; 1.31]	385 167/736
Lag time 24 months		
No exposure	1.00 (ref)	280 990/287
Exposure	1.22 [1.05; 1.41]	355 115/526

* Lag time 1 year, fully adjusted for sex; age; polypharmacy (defined as prescription of five or more different drugs); prescription of low-dose acetylsalicylic acid (ASA), non-ASA non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors, statins, spironolactone, glucocorticoids for systemic use, selective serotonin reuptake inhibitors, and hormone replacement therapy; the comorbidities diabetes, chronic obstructive pulmonary disease, congestive heart failure, and alcohol-related diseases; the Charlson comorbidity index (score); and prevalent valsartan use
95% CI, 95% confidence interval

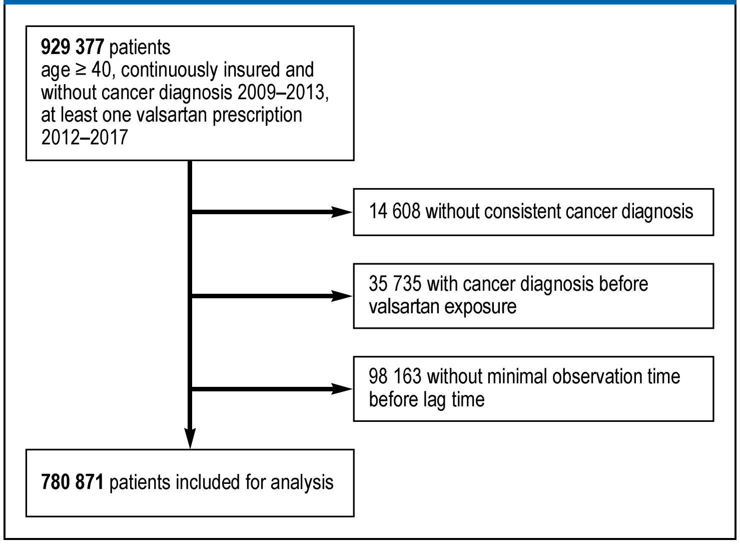
eTABLE 3

ATC codes*[1] and ICD-10 codes*[2]

Substance		
Valsartan	ATC	C09CA03, C09DA03, C09DA23, C09DB01, C09DB08, C09DX01, C09DX02, C09DX04, C09DX05, C09DX10
Acetylsalicylic acid	ATC	B01AC06, B01AC30, B01AC34, B01AC36, B01AC56, B01AC86, C07FX02, C07FX03, C07FX04, C10BX01, C10BX02, C10BX04, C10BX05, C10BX06, C10BX08, C10BX12, N02BA01, N02BA51, N02BA71
Non-steroidal anti-inflammatory drugs	ATC	M01A
5α-Reductase inhibitors	ATC	G04CB01, G04CB02, G04CA51, G04CA52
Statins	ATC	C10AA, C10BA, C10BX
Spironolactone	ATC	C03DA01, C03EC01, C03EC21, C03EC41, C03ED01
Glucocorticoids	ATC	H02AB
Hormone replacement therapy	ATC	G03C excl. G03CD, G03DA, G03DB, G03DC, G03EA03, G03F
Selective serotonine reuptake inhibitors	ATC	N06AB, N06CA03
Cancer outcomes		
All cancer	ICD10	C00–C96 excl. C44
Colon cancer	ICD10	C18–C20
Liver cancer	ICD10	C22
Pancreatic cancer	ICD10	C25
Lung cancer	ICD10	C34
Malignant melanoma	ICD10	C43
Breast cancer	ICD10	C50
Uterine cancer	ICD10	C54, C55
Prostate cancer	ICD10	C61
Kidney cancer	ICD10	C64
Bladder cancer	ICD10	C67
Comorbidities		
Diabetes	ICD10	E10–E14
Chronic obstructive pulmonary disease	ICD10	J42–J44
Congestive heart failure	ICD10	I11.0, I13.0, I13.2, I42, I43, I50, I51.7
Alcohol-related disease	ICD10	E244, G31.2, G62.1, G72.1, I42.6, F10.2, K29.2, K70, K86.0, T51.9, Z502, Z72.0

*[1] ATC codes according to the Anatomical Therapeutic Chemical classification system
*[2] ICD-10 codes according to the International Classification of Diseases and Related Health Problems, 10th revision, German modification

eFIGURE



Overview of study cohort after application of the selection and data quality control criteria

Exhibit K

Evidence-Based Toxicology: "Sound Science" in New Disguise

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EXHIBIT

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Evidence-Based Toxicology: "Sound Science" in New Disguise

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The "evidence-based toxicology" proposed by Guzelian et al. departs radically from state-of-the-art toxicology by claiming that risks for humans can only be determined on the basis of human evidence. Just like the previous proposal of "sound science," "evidence-based toxicology" poses a heavy burden of proof on any effort to control exposures in order to reduce health risks to those exposed. The alleged connection between "evidence-based toxicology" and evidence-based medicine is misconceived, since the strict criteria for use of scientific data in evidence-based medicine concerns proof of therapeutic effects, while in "evidence-based toxicology" these criteria are applied to proof of harmful effects. The slogans "sound science" and "evidence-based toxicology" have both been put forward by persons with a history of extensive involvement with the tobacco industry. *Key words*: Evidence-based toxicology; evidence-based medicine; risk assessment; burden of proof; sound science; bias; Philip S. Guzelian; tobacco; Philip Morris.

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Few things could be less controversial among toxicologists than the principle that toxicology should be based on scientific (empirical) evidence. Almost equally uncontroversial is the viewpoint that toxicological risk assessment can be improved by the adoption of methods for systematic review similar to those that have been developed in evidence-based medicine (EBM). Neither of these principles is at issue here. Instead, we challenge the recent paper by Guzelian et al. which, under the guise of "evidence-based toxicology," (EBT) proposes to limit the definition of "risk" to include only risks that have been epidemiologically proven in humans. Attempts are currently made to create a movement for the reform of toxicological practices along these lines. An "International Forum Towards Evidence-Based Toxicology" organized by a group of individual scientists and supported by ECVAM (European Center for the Validation of Alternative Methods) was held in October 2007. The purpose of this meeting was "to explore the available concepts of evidence-based toxicology (EBT) and to launch an initiative to formally implement evidence-based assessment methods."[1,2]

If Guzelian et al.'s proposals were to be implemented it would have drastic implications for current risk assessment practices. Thus, it is important to scrutinize both the underpinnings and the implications of Guzelian et al.'s proposal. In this paper we report our investigation of the "evidence-based toxicology" of Guzelian and coworkers. Our primary source is their 2005 article[3] that provides the most systematic presentation of their ideas. In what follows, page references in brackets refer to this article.

Guzelian et al. present their proposal as a rather direct application of the principles of EBM to the subject matter of toxicology (p. 161). As we will show, this is far from correct. To the contrary, their proposal departs radically from principles shared by EBM and state-of-the-art toxicology. First, we scrutinize Guzelian et al.'s concepts of risk and causality and investigate their implications. Then, we compare their approach with that of EBM. We also discuss the implications of Guzelian et al.'s views on data generated from animal and other non-human experiments. Finally, we trace the intellectual origins of their proposal.

IMPLICATIONS OF GUZELIAN ET AL.'S DEFINITIONS OF RISK AND CAUSALITY

Causality has an important role in Guzelian et al.'s approach to risk. A principal tenet is that "only known possibilities (established causal relationships termed epistemic possibilities) should be deemed 'risks'" (p. 164). In their view, the identification of a risk for humans requires that a causal relationship between exposure and effect has been established in humans:

> Thus, for a toxicologist to determine a risk for humans, it must be known that the Hazard can occur under the circumstances relevant to such toxicological principles as dose or route of exposure, and it must be known how frequently such a Hazard has been observed to occur in humans under these circumstances."(p. 162).

The interpretation of these statements requires attention to the authors' somewhat unusual terminology. Guzelian et al. define "epistemic" as a synonym of "known" (p. 192). This deviates from the standard meaning of the word "epistemic," namely, "of or relat-

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ing to knowledge or degree of acceptance" (Oxford English Dictionary). Furthermore, they declare that they use "risk" and "epistemic risk" synonymously (p. 192). It follows directly from these definitions that Guzelian et al. treat "risk" and "known risk" synonymously. Hence, their definitions have the strange consequence that there can be no unknown risks.

These definitions are in opposition to common usage in toxicology. Risk assessors frequently describe risks in terms of probability estimates such as "possible" and "likely" risks, and use standardized hazard descriptors such as: "Likely to Be Carcinogenic to Humans," "Suggestive Evidence of Carcinogenic Potential," "Inadequate Information to Assess Carcinogenic Potential," "Not Likely to Be Carcinogenic to Humans,"[4] "Sufficient evidence of carcinogenicity," and, "Limited evidence of carcinogenicity."[5,6]

Guzelian et al. use a variety of terms to denote that which they exclude from the definition of risk: "only hypothesized or conjectured harmful outcomes" (p. 162), "mere nomological possibility" (p. 162), "uncertainty" (p. 166), "authority-based opinion" (p. 179), etc. They maintain that the term "risk" should only be used when there is a "known causal relationship between a stimulus and the undesirable effect or outcome" (p.162). In principle this would require experimental studies on humans, but they concede that

> a similar set of characteristics, popularly called the 'Hill Criteria', make it possible, if knowledge is robust, to infer causation from only observational (non-experimental) studies, where allocation of test subjects or items is not under the control of the investigator (p. 161).

In referring to the "Hill Criteria," Guzelian et al. suggest that, traditionally, a set of criteria had be satisfied to establish causality; and that those criteria were established by Sir Austin Bradford Hill. However, no fixed set of criteria has ever been accepted as being necessary to establish causation.[7] Indeed, in his landmark article, Hill referred to the nine factors to be considered in determining causality as "viewpoints," and eschewed the notion that they were "requirements" or "criteria":

> Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe—and this has been suggested—is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question—is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?[8]

Referring to the "Hill criteria" (e.g., p. 168), Guzelian et al. state that "evidence-based toxicology" suggests that the following criteria be satisfied before "an evidence-based conclusion" of toxicity can be made:

1. High quality epidemiological studies should generally show a relative risk of three or greater.
2. The positive epidemiological results should be replicated among high quality studies and repeated across multiple designs.
3. The epidemiological studies should each measure the same chemical cause (exposure to one and the same chemical) and the same, specified, health outcome ("hepatic steatosis is not the necessarily same as 'liver injury'").
4. "[T]he mechanisms and/or doses shown to be involved in animal chemical carcinogenesis [should] also be known to operate in humans" (pp. 186–7).

For the criterion of a relative risk of three, Guzelian et al. refer to a News Report (not a scientific paper) in *Science* by Gary Taubes in which the reporter states that "most epidemiologists interviewed by *Science* said that they would not take seriously a single [epidemiology] study reporting a new potential cause of cancer unless it reported that exposure to the agent in question increased a person's risk by at least a factor of 3—which is to say it carries a risk ratio of 3."[9] Since this is a news article, it is no surprise that it does not contain any of the in-depth discussion of statistical and other issues that is needed to determine the evidential value of results with different risk ratios, and Guzelian et al. do not mention the critical discussion that followed the publication of this news report. In an invited comment to Taubes in the *American Journal of Epidemiology*, Ernst L. Wynder stated:

> One cannot agree that any relative risk of less than 2 and certainly not of 3 or 4 should be neglected. Even a relative risk of 1.2 or 1.3, if epidemiologically established as a causative factor, can have a major public health impact.[10]

As Wynder points out, it is neither common practice nor scientifically accurate to require a risk ratio of three or more before a causal connection is accepted. For instance, applying this criterion would seem to dismiss cigarette smoke as a risk factor for ischaemic heart disease. Doll et al.'s fifty year follow-up study reports that heavy smokers have a slightly less than doubled age-standardized mortality rate for ischaemic heart disease compared to never-smokers.[11] Since this is a common disease and a common exposure, a near doubling of the risk will result in a significant increase in the number of deaths. The same scenario could apply to a chemical with wide-spread use and exposure. The risk ratio is only one of several factors to be taken into

account in the evaluation of an epidemiological study. Results showing a small increase in relative risk from a high quality study with excellent control of confounders may be more reliable than results with a high relative risk from a study with insufficient control of confounders.

If Guzelian et al.'s criteria were to be implemented for the purpose of toxicological risk assessment, this would have radical implications for public health, as can be seen from the following pronouncement:

> As with EBM, flaws in framing the EBT question can lead to unhelpful or even misleading answers from the literature. For example, a 'hazard assessment' as called for by the National Academy of Science in its four-step protocol for risk assessment amounts to an all-inclusive recitation of known or suspected toxic effects of a chemical irrespective of such qualifying circumstances as human versus animal, exposure route, dose, etc. Undertaking such a critical review can be daunting if the literature is voluminous and is likely to return irrelevancies (p. 181).

This line of argument is nothing less than a denunciation of state-of-the-art toxicological risk assessments. The generally accepted ideal for such assessments follows the pattern endorsed by the National Academy of Sciences.[12,13] Such risk assessments should be based on a careful collection and evaluation of all the relevant evidence of sufficient scientific quality, including human, animal, *in vitro*, and other types of data, in an overall assessment that describes both the established and the likely health effects that different exposures to the agent in question can cause. Major organizations conducting state-of-the-art toxicological risk assessments have repeatedly emphasized the importance of collecting and combining all the relevant evidence, including both studies of animal models and studies of effects in exposed humans.[14–16]

The careful evaluation of mode of action, exposure route, dose, and other information to clarify the relevance of animal-to-human extrapolations is an essential part of standard risk assessment procedures. The IPCS and the Human Relevance Framework have proposed a systematic framework for incorporating data on mode of action in the risk assessment process.[17,18] The proposed process relies on data from animal, human and other types of studies, and rests on the default assumption that animal data are treated as relevant to human hazard and risk assessment unless there is sufficient evidence to the contrary. It is this type of state-of-the-art procedure that Guzelian et al. dismiss as "unhelpful or even misleading" and as "likely to return irrelevancies." The major difference between state-of-the-art toxicological risk assessments and Guzelian et al.'s "evidence-based toxicology" is that the latter, if fully implemented, deprives risk assessors of most toxicological evidence.

The potential implications for risk management of Guzelian et al.'s proposal are momentous, since only a small part of the protective measures taken by companies and regulatory agencies are based on what Guzelian et al. call "risk." Of course, the degree of protection that a risk management policy offers against possible dangers identified in animal experiments does not depend on whether or not these possible dangers are called "risks." This is also recognized by Guzelian et al.:

> Of course, many regulatory agencies, public advocacy groups, crisis managers and safety experts advise that certain actions (such as evacuations, waste cleanups, restricted product usage, etc.) be taken to reduce 'risks' even if the possibility of harm is only nomological. Such pragmatic actions may be defended by policy considerations such as reference to the Precautionary Principle: It is better to be safe than sorry. However, treating uncertainties as if they were risks, out of an abundance of caution, is wholly distinguishable from stating that those nomological possibilities are epistemic and represent risks. Such practices raise ethical concerns even if the cause is just (e.g., protecting the public). It may not be acceptable to use the deception of advancing a social policy cloaked as scientifically established fact, to achieve the justice being sought (p. 166).

Given their highly restrictive definition of risk, it is remarkable that Guzelian et al. describe action against "non-risks" in their sense as based on "an abundance of caution."

Current practices of classifying and labelling substances according to their hazardous properties provide a good example of the implications of applying the criteria proposed in "evidence-based toxicology." Classification and labelling is a central element in most developed systems of chemical risk management. The various systems used in different regions such as the European system[19] and the coming Globally Harmonized System for classification and labelling of chemicals, GHS (http://www.unece.org), are all based on processes and criteria that make extensive use of animal, *in vitro* and other experimental data. The number of substances and exposures classified by these systems would be drastically reduced if the use of non-human data for hazard and risk identification were discontinued.

The classification of carcinogens as performed, for instance, by the European Union and by the International Agency for Research on Cancer (IARC) provides a particularly instructive comparison between current practices in the identification of hazard and risk and those proposed by Guzelian et al. In the current European system for the classification of carcinogens, Guzelian et al.'s criteria can in practice only be satisfied by substances classified in Category 1. Classifications in this category have to be based on positive and conclu-

TABLE 1 Categories and Corresponding Criteria for Carcinogenicity Classifications According to European Council Dir 67/548 (as Amended by Dir 2001/59)*

Category 1 carcinogens

"Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer."

Category 2 carcinogens

"Substances which should be regarded as if they are carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:

- appropriate long-term animal studies,
- other relevant information."

Category 3 carcinogens

"Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in category 2."

*Commission Directive 2001/59/EC of 6 August 2001adapting to technical progress for the 28th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances Official Journal of the European Communities L 225/1 21.8.2001.

sive epidemiological data, while classifications in Categories 2 and 3 can be based on animal data alone or on a combination of human and other data (Table 1). (The same general principle applies also to classifications of mutagens and reproductive toxicants). Similarly, in the IARC's classification system for carcinogens, Guzelian et al.'s criteria can only be satisfied by substances classified in Group 1, "The agent is carcinogenic to humans," for which conclusive human data is required (Table 2). However, neither IARC nor the European directive specifies a minimum risk ratio or the number of studies (across different designs) that are needed. Therefore, some of the substances classified in Category/Group 1 in the respective system might not satisfy the criteria proposed by Guzelian et al. In any event, at most 8% of the substances classified as either carcinogens or potential carcinogens in the European Union, and at most 11% of the agents

TABLE 2 IARC's Classification Groups and the Corresponding Criteria for Carcinogens

Group 1: The agent is carcinogenic to humans.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans.

Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is limited evidence of carcinogenicity in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents for which the evidence of carcinogenicity is inadequate in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

TABLE 3 The Distribution of (Potentially) Carcinogenic, Mutagenic, and Reproductive Toxicant Substances between the Three Classification Groups for Such Substances Categorized within the European Union, as of 2005 (www.kemi.se, March 2008). Total Number of Classified (Single) Substances = 594.

Category	Carcinogens	Mutagens	Reproductive Toxicants
1	24 (8%)	0 (0%)	17 (9%)
2	151 (50%)	31 (29%)	65 (35%)
3	126 (42%)	77 (71%)	103 (56%)
Sum	301	108	185

TABLE 4 The Distribution of (Potentially) Carcinogenic Agents between the Classification Groups Categorized by IARC (www.iarc.fr, August 2008).

Category	Number of Agents
1	105 (11%)
2A	66 (7%)
2B	248 (27%)
3	515 (55%)
4	1 (–)
Sum	935

(including chemicals, viruses, mixtures, and exposure scenarios) classified as such by the IARC satisfy the criteria of Guzelian et al.'s "evidence-based toxicology" (Tables 3 and 4).

"EVIDENCE-BASED TOXICOLOGY" VS. EVIDENCE-BASED MEDICINE

EBM is a relatively new methodology, developed in the 1990s to improve the use of scientific evidence and further the goals of medicine, namely to protect and restore human health. The essence of EBM is the systematic review of all available evidence based on consistent ranking systems that classify clinical studies according to their quality and their relevance for clinical medicine. Guzelian et al. claim that they apply the principles of EBM directly to toxicology (p. 161). The connection between EBM and EBT is further explained on the EBT web-page (www.ebtox.org):

> Over the last two decades clinical medicine has developed a new approach ("evidence-based medicine") seeking to ensure that any decision for patients' health is based on the best scientific evidence available. Similarly, toxicology might embrace an "evidence-based toxicology": the best possible scientific evidence shall be applied to assess testing tools in an evidence-based manner and for using results generated by these tools again in an evidence-based manner for making decisions on product safety and likely risks to humans and environment.

Despite their appeal to EBM and appropriation of its terminology, what Guzelian et al. really do is to apply its principles inversely: They take the criteria used in EBM for the proof of therapeutic effects, and apply these same criteria in what they call "evidence-based toxicology," but for adverse effects.

EBM serves the general principles of medical practice, namely that the positive effects of therapy must always outweigh any adverse effects. EBM is thus concerned with both therapeutic effects and (negative) side effects of drugs. It is also part of a larger system of medical research and evaluation in which toxic effects on laboratory animals are taken as indicative of corresponding effects on humans. The pre-marketing data requirements for pharmaceutical compounds are extensive and rely heavily on the use of experimental animals. These animal data have a central role, both to show the effectiveness of the drug in interacting with the intended biological target and for the early identification of potential adverse side effects. Due to these test requirements, a rather large amount of animal toxicity data has to be produced before a drug may be used in a clinical trial. This includes sufficient documentation of therapeutic effects, characterization of its mechanisms of pharmacological action, toxicity testing, and when relevant, long-term and carcinogenicity testing.[20] Based on these animal data, the development of some potential drugs is terminated, and they are never administered to humans. The reason evidence-based medicine focuses on studies on humans is that only those substances that have already shown acceptable safety and efficacy based on animal data are admitted to clinical trials in humans. Clinical trials of pharmaceuticals with no animal toxicity data have long since been regarded as unethical by all major medical organizations and authorities such as the European Medicines Agency and the U.S. Food and Drug Administration.

It should be obvious that the principles of EBM are opposed to the principles of EBT and cannot in any way be used as an argument for allowing significant human exposure to chemical substances, whether pharmaceuticals or other types of compounds, that have not been subject to toxicity testing or for which animal tests indicate that the substance is highly toxic. Guzelian et al.'s attempt to use EBM, with its strong reliance on prior animal testing, as an argument for dismissing animal data from risk assessment, is such a bizarre argument that it was initially a riddle for us how it could at all be seriously put forward. (We will return to the solution of this riddle.)

Apart from this, what would it mean to apply the principles of EBM to toxicology? The most logical way to do so would be to apply in toxicology the criteria that are used in EBM for adverse drug effects. The following simple example illustrates this: A new food preservative is proposed. Convincing evidence shows that the substance is a potent carcinogen in rodents.[21] The mechanism of carcinogenesis is insufficiently under-

stood and there is no data from human exposure. If we apply the principles of EBM to this example, the use of this new food preservative, leading to wide-spread human exposures, will simply not be allowed. Given the available rodent carcinogenicity studies, a decision to allow marketing of the substance would be considered unethical, and not supported by regulatory agencies. If we instead apply Guzelian et al.'s risk criteria, the conclusion would be quite different. In their terminology, this is a clear case of "no risk." Therefore, unless an "abundance of caution" (p. 166) is applied, the substance will be subject to no restrictions based on the rodent carcinogenicity data. The substance will not be considered a risk to humans until sufficient exposure of humans has taken place to generate evidence of carcinogenic activity in humans repeatedly in studies over multiple designs and with a relative risk of 3 or greater (p. 187). As this example shows, the disregard for animal evidence that Guzelian et al. promote under the name of "evidence-based toxicology" is as alien to evidence-based medicine as it is to state-of-the-art toxicological risk assessment.

Guzelian et al.'s inverse application of EBM principles is perhaps most clearly seen in their reference to Herrington's and Howard's careful discussion of the widespread prescription of postmenopausal hormone therapy in the U.S. based on the hypothesis that such therapy might reduce women's risk of coronary heart disease.[22] This hypothesis was subsequently rejected due to the generation of evidence from randomized clinical trials that failed to establish a connection between hormone therapy and a decrease in the risk of coronary heart disease. In their paper, Herrington and Howard warn against the use of unsubstantiated hypotheses to develop broad treatment recommendations, and they emphasize that "observational or mechanistic studies, animal models, and basic research have tremendous value for the generation of hypotheses but should not be used to justify broad-based pharmacological interventions." After quoting this phrase, Guzelian et al. state: "It is not difficult to see the same mistake in the field of occupational and environmental toxicology, in which clinical data are sometimes sparse and experts sometimes cobble up causal inferences from observed effects of chemicals *in vitro* or in animals (or both), often at high doses" (p. 175). While Herrington and Howard argue in favour of strict evidentiary criteria for treating a substance as beneficial, Guzelian et al. construe this argument as implying similarly strict criteria of evidence for treating a substance as harmful. (Concerning the use of "high doses" in animal experiments, see Bucher 2002.[23])

HOW USEFUL IS ANIMAL EVIDENCE?

Guzelian et al. express a far-reaching scepticism of animal models. Interestingly enough, their scepticism seems to apply only to the use of animal models for the identification and quantification of toxic effects, not to their use for elucidating pharmacological activity or toxic mechanisms:

> Animal and in vitro systems also produce experimental results pertaining to toxic phenomena, but carry uncertainty because of questions of applicability of the results to humans. The value of such experimental knowledge lies in understanding basic pathophysiology and mechanisms of toxicity, which can aid in understanding human disease (p. 183).

Unfortunately they do not offer any explanation of why animal data can provide reliable data on toxicological mechanisms to be used in human risk assessment, while at the same time such data are too unreliable to be used for hazard or risk identification.

All toxicologists are aware that interspecies correlations in toxicity are not perfect and that data from animal experiments may over- or underestimate actual human risk. The relevant question is therefore not whether these models are perfect but whether the information they provide is sufficiently plausible to be used in risk assessment. This in turn, will of course ultimately depend on risk managers' tolerance levels for false positives and negatives, which are matters of policy rather than scientific questions.

The political aspects of risk management can be seen very clearly in Guzelian et al.'s use of Olson et al.'s[24] study that compares the toxicity of pharmaceuticals in humans and animals. Guzelian et al. write:

> Indeed, Olson et al. found a 'true positive concordance rate' (sensitivity) of only 70% when preclinical animal studies in all test species (43% for rodents only) were compared to the observed human toxicities in subsequent clinical trials (broadly interpreted as an adverse event involving the same organ)."(p.186)

The small word "only" in "only 70%" is essential here. For Guzelian et al. it is an argument against the use of animal models if only 70% of these toxic effects demonstrated in humans were previously shown in animals. However, 70% is only a small proportion if the risk assessments serve a risk management policy that prefers non-regulation to regulation based on information with this level of accuracy. In our experience, many risk managers both in industry and government agencies would, to the contrary, prefer to act on such information rather than refraining from protective measures. Olson et al. themselves conclude that their study results "support the value of in vivo toxicology studies to predict for many significant [human toxicities] associated with pharmaceuticals [. . .]"[24] (The interpretation of this study is complicated by the fact that only substances that had reached clinical trials were

included. Olson et al. themselves say: "This study did not attempt to assess the predictability of preclinical experimental data to humans. What it evaluated was the concordance between adverse findings in clinical data [and] data which had been generated in experimental animals (preclinical toxicology).")

Exclusive reliance on the type of human evidence that Guzelian et al. refer to makes sense if the only concern is to avoid false positives. However, if false negatives are also a concern, then this approach is not optimal. The risk of false negatives is substantial even in large, well-conducted epidemiological studies. This is, of course, one of the major reasons why animal and *in vitro* experiments are performed at all. They reduce the risk of false negatives at the price of an increased number of false positives. This is a price that most risk managers—and most persons exposed to chemicals – seem to be willing to pay.

THE ORIGINS OF "EVIDENCE-BASED TOXICOLOGY"

As should be clear from the above, Guzelian et al.'s views on risk assessment are implausible and not mainstream when considered in relation to well-established principles in toxicological risk assessment. We initially found it inexplicable how such an extreme view of risk assessment, and one that deviates so blatantly from evidence-based medicine, could be proposed seriously at all, especially with the claim of being "evidence-based." We were able to understand this only after tracing the intellectual origins of "evidence-based toxicology."

Guzelian et al.'s proposal is connected to both the tobacco industry and to litigation concerning potential occupational toxic injuries. Beginning with the former, the tobacco industry has a long history of neglecting and distorting scientific evidence. In 1993, Philip Morris started and funded an ostensibly independent organization called The Advancement of Sound Science Coalition (TASSC).[25] Its major purpose was to discredit the then rapidly accumulating evidence that passive smoking has negative health effects.[26] The term "sound science" was launched by TASSC as a slogan for the position that no action should be taken against a possible danger until full scientific proof of that danger has been obtained.[27] This view on the burden of proof essentially coincides with the risk management implications of Guzelian et al.'s "evidence-based toxicology." The notion of "sound science" has now been thoroughly discredited. It appears that "evidence-based toxicology" is an attempt to relaunch the same controversial principle, again under a name that sounds uncontroversial.

Philip S. Guzelian has a background as a consultant for the tobacco industry. During his time affiliated with Philip Morris he was paid about $100,000 per year.[28]

The second connection concerns Philip S. Guzelian's litigation activities concerning potential occupation . He acts regularly as an expert giving testimony in litigation matters when workers claim to have sustained an occupational toxic injury. According to his own estimate, he has given depositions on average four times a year during the last twenty years, and he has testified in court trials on average 2–3 times a year.[29] For all of his medico-legal work he has received approximately $500,000 to 1,000,000 per year according to his own testimony.[30] In all these cases but one has he testified on behalf of an industry defendant.

In 2004 he joined the Advisory Council of the Atlantic Legal Foundation,[31] an organization that still uses the term "sound science" in describing its principles for legal evidence.[32] It is clear from transcripts of Philip S. Guzelian's depositions that he acts efficiently in the interests of his corporate clients.[29,33] In his assessments of workers' claims that their diseases are work-related, he applies the same exceptionally high standards of evidence that are proposed in Guzelian et al. (2005).

CONCLUSION

Guzelian et al. claim that they apply the principles of EBM directly to toxicology. However, what they really do is apply these principles inversely: They take the criteria used in EBM for proof of therapeutic effects, and apply these same criteria in what they call "evidence-based toxicology" but for adverse effects. When doing this they dismiss evidence from animal models, only accepting conclusive epidemiology as evidence of risks in humans. Guzelian et al.'s proposal departs radically from principles that are shared by evidence-based medicine and state-of-the-art toxicology. Its application would in fact deprive risk assessors of most of the toxicological evidence that is now accessible to them. The use of the term "evidence-based" for such a move is grossly misleading.

"Evidence-based toxicology" poses a very heavy burden of proof on those attempting to prevent or reduce toxic exposures. It does so in the same way as the previous proposal of "sound science" (another misnomer). The two slogans "sound science" and "evidence-based toxicology" have both been put forward by persons with a long history of extensive involvement with the tobacco industry. Toxicological risk assessment certainly needs new ideas and fresh breezes, but we should not expect fresh breezes to come from those quarters.

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Erratum

The Volume 14, Number 3 (October/December) issue of *IJOEH* contained an error in the spelling of the name of one author of "Surveillance for Early Silicosis in High Altitude Miners Using Pulse Oximetry." The authors should have appeared as: Joseph A Donroe, MD, MPH, Paola J Maurtua-Neumann, MD, Robert H Gilman, MD, Ana Teresa Acosta, MD, Gene Caine, MD, John E Parker, MD, Jaime Carlos Alvarez Carhuaricra, MD, Juan Jose Retimozo Padilla, MD, Daniel Mendoza, MD, Mirko Zimic, PhD, David A.J. Moore, MD.

Exhibit L

Special issue

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Evidence-based causation in toxicology: A 10-year retrospective

RC James[1], JK Britt[2], NC Halmes[3] and PS Guzelian[4]

Abstract

We introduced Evidence-based Toxicology (EBT) in 2005 to address the disparities that exist between the various Weight-of-Evidence (WOE) methods typically applied in the regulatory hazard decision-making arena and urged toxicologists to adopt the evidence-based guidelines long-utilized in medicine (i.e., Evidence-Based Medicine or EBM). This review of the activities leading to the adoption of evidence-based methods and EBT during the last decade demonstrates how fundamental concepts that form EBT, such as the use of systematic reviews to capture and consider all available information, are improving toxicological evaluations performed by various groups and agencies. We reiterate how the EBT framework, a process that provides a method for performing human chemical causation analyses in an objective, transparent and reproducible manner, differs significantly from past and current regulatory WOE approaches. We also discuss why the uncertainties associated with regulatory WOE schemes lead to a definition of the term "risk" that contains unquantifiable uncertainties not present in this term as it is used in epidemiology and medicine. We believe this distinctly different meaning of "risk" should be clearly conveyed to those not familiar with this difference (e.g., the lay public), when theoretical/nomologic risks associated with chemical-induced toxicities are presented outside of regulatory and related scientific parlance.

Keywords

Evidence-based toxicology, causation, evidence-based logic

Causality has been variously discussed, defined, and debated since the early Greek philosophers and has been an important concept in toxicology and all phases of human health advancement. Although this concept has been acknowledged for much of recorded human history, it became a more focal concern in modern times, beginning in the 18th century when Sir Percivall Pott noted that chimney sweeps had a high incidence of scrotal cancer. As medicine and toxicology advanced in the mid-20th century, a set of criteria developed by Bradford Hill has become the accepted standard for causal inference of observational data.[1,2] But recently this methodology has been improved upon by a more rigorous causation methodology known as evidence-based medicine (EBM). The introduction of evidence-based logic and guidelines quickly became the accepted standard of practice in medicine for reaching scientific decisions about questions of diagnosis, disease management, prevention and treatment, and the efficacy or harm of chemicals or agents used therapeutically and was soon recognized as one of the major milestones in the history of medicine. Seeing the gap between the development and widespread acceptance of evidence-based methods in medicine and the regulatory hazard decision-making process of weight-of-evidence (WOE) schemes used in environmental regulatory toxicology, we introduced evidence-based toxicology (EBT) in 2005. This was a comprehensive framework for performing transparent, auditable, and reproducible causation analyses for chemical exposures that may induce human disease.[3]

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EBM is the conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients.[4] Knowledge about current best evidence is gained from a rule-based systematic review of all the applicable medical literature. We applied these same principles to toxicologic causation analysis and called for a parallel method that involved the systematic review and analysis of the scientific literature encompassed in three steps: (1) ask an appropriate question; (2) perform a comprehensive review and assemble the literature that address that specific question; and (3) using a predetermined quality instrument, rate, rank, and analyze the studies in a manner that provides the appropriate evidence to answer the question. Since our initial publication on EBT in 2005 there has been a continued and growing interest in EBT.[5–8] The Johns Hopkins University created an endowed chair in EBT that focused on evidence-based principles to improve and validate testing methods in animals.[9] The US Food and Drug Administration adopts the same evidence-based principles for determining the acceptability of health claims.[10,11] The Society of Toxicology has held several meetings related to EBT at or in conjunction with their annual meetings.[12–15] The first step in any evidence-based analysis, that of producing a comprehensive, systematic review to address specific questions in toxicology, has now gained acceptance in the international toxicology community.[16–19]

However, the term "evidence-based" in toxicology, as in medicine, has led to misunderstandings as scientists always believe they have relied on the available evidence. For example, the EBM, EBT, and Hill criteria causation methodologies we would argue were never a type or variation of the regulatory WOE method as some have erroneously listed it, but like us, Hartung, the other early proponent of EBT methods, have noted that past WOE schemes were the very antithesis of basic EBM/EBT principles and methods.[20,21] In a similar vein, while our original article stated (and we still accept as true) that human data are the most valid metric to determine human causality, EBT does not call for eliminating the consideration of animal studies. In fact, our publications have consistently argued that when human data are insufficient to answer human causation and human risk questions, the regulatory risk assessment process will derive conservative, health-protective exposure guidelines in the interim.[3,22–24] However, in the interest of providing greater transparency and accuracy in risk communication, we have proposed that regulatory agencies should be more explicit in informing the general public when their decisions do not represent a human-based causation determination but rely only on nonhuman data. In this situation, the possible hazard and associated "risk estimate" are only presumed expressions that contain an unknowable degree of uncertainty. This uncertainty is then used in regulatory risk assessments in a manner that ensures these regulatory guidelines and criteria are protective (but not predictive) of the actual human health outcome from a specific chemical exposure.[3,22–25]

We note, despite recent advances in evidence-based causation methods, recent views discussing causation methodology continue to advocate dated practices and analytical methods to assess causation,[25] for example, blending causation concepts with environmental regulatory acronyms and argot generated decades ago to support specific regulatory needs. So, we would point out that "causation/hazard" classification and human "risk/uncertainty" estimates are two examples where regulatory terminology seems to have ambiguated the medical and epidemiological use of these terms. For example, the default regulatory approach altered the method for identifying true human health hazards (i.e. known risk factors) by combining nomologic (animal data) and epistemic (epidemiology) information in their WOE classifications of the hazard (e.g. carcinogenicity). Figure 1 is a graphical representation of this process.

In regulatory-like WOE approaches, the final decision as to what combination of toxicological and epidemiological data is considered to represent sufficient evidence of causation is decided by the authoritative opinion. Because different combinations of human and animal data are used, the outcome is frequently a nomologic hazard/risk conclusion. The analysis is performed in a nontransparent, unauditable, and post hoc manner. This has led to biased conclusions in the past based on a less than complete acquisition of all available data.[29] Yet the WOE approach has been pervasive in the US Environmental Protection Agency (USEPA) regulatory documents; for example, Lutter et al. report that this terminology was stated 37 times in the USEPA's 2005 Carcinogen Risk Assessment Guidance.[30] WOE is a term that implies a specific, objective method is being used when that is not always the case. In fact, one of the major limitations of the WOE concept in the past has been that there is no single definition for WOE.[26,27] When 52 different WOE causation frameworks were systematically analyzed, no two contained the same process elements.[17] Still, others have noted that the

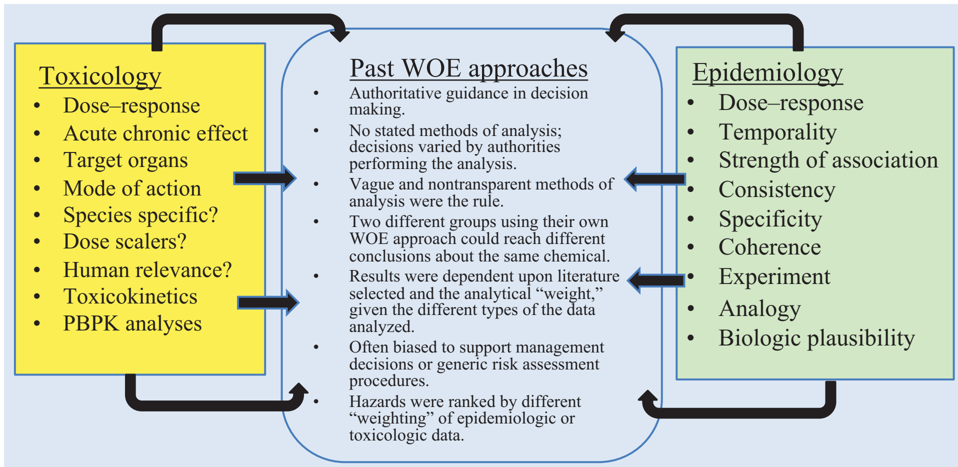

Figure 1. The Regulatory WOE Methodologies (Adapted from figures or concepts in the works by Weed, Krimsky, and Adami et al.[26–28]). WOE: weight-of-evidence.

regulatory WOE approach is essentially the antithesis of the evidence-based methods for determining causation, which were first adopted in medicine and then recommended for toxicology.[3,20,21]

Perhaps mindful of the linguistic and structural shortcomings of the past WOE schemes, Rhomberg and coworkers have recently developed a new type of WOE analysis methodology that has a different objective.[30,31] Its purpose is to identify data gaps in the evidence supporting or contradicting the specified hypothesis. Interestingly, this type of WOE adopts some of the basic components of EBT, as outlined by Guzelian et al., and attempts to move WOE analyses from authoritative opinion/policy decisions toward a more evidence-based type of analysis where the amount and quality of the available evidence support or does not support the hypothesis being evaluated.[3] However, like the past WOE approaches, some decisions may still be derived solely from animal data and, therefore, contain the same species extrapolation uncertainties that apply to former regulatory approaches. Still, its adoption of some EBT causation principles, including better transparency, introduces a marked improvement over the past regulatory WOE assessments.

Our comprehensive framework, calling for the use of evidence-based logic to determine causal inference in toxicology, discussed the steps and procedures for reaching causal opinions consistent with that now applied in medicine. A graphical representation of how causal inference is established with this methodology is shown in Figure 2.

The focus of this approach is the application of a systematic collection of all pertinent available data and an objective methodology that evaluates the epidemiology data using an a priori set of guidelines for rating and ranking the findings of each study. In this manner, the available data itself establish whether there currently exists sufficient evidence to establish a causal linkage or not. As Figure 2 shows, in EBM and EBT, the emphasis is placed on epidemiologic evidence. In causation, the role of animal toxicology is to create/support the single Hill criterion of biologic plausibility. Here animal data may help direct the design of future epidemiology studies, provide mechanistic analyses, or provide for other comparative analyses of available epidemiologic and animal investigations. The push to adopt evidence-based principles to improve animal toxicity testing, initiated by Hartung at the Center for Alternatives to Animal Testing, should also lead to improvement in the use of animal data by leading to a better predictive value of the potential human health effects derived from specific toxicity tests.

Such efforts are needed because animal extrapolations may introduce uncertainties that adversely impact the accuracy of a hazard identification (*qualitative extrapolation uncertainty*) or its dose-related probability of occurrence (*quantitative extrapolation uncertainty*). Even the mechanistic/mode-of-action data can be misleading (*mechanistic uncertainty*) if the animal species (or strain) chosen to study a biologic pathway of interest fails to reflect the actual human pathway.[31] In short, the evidence-based method for human causation recognizes and utilizes the helpful insights that animal studies may provide without allowing the uncertainties inherent to each animal-to-man

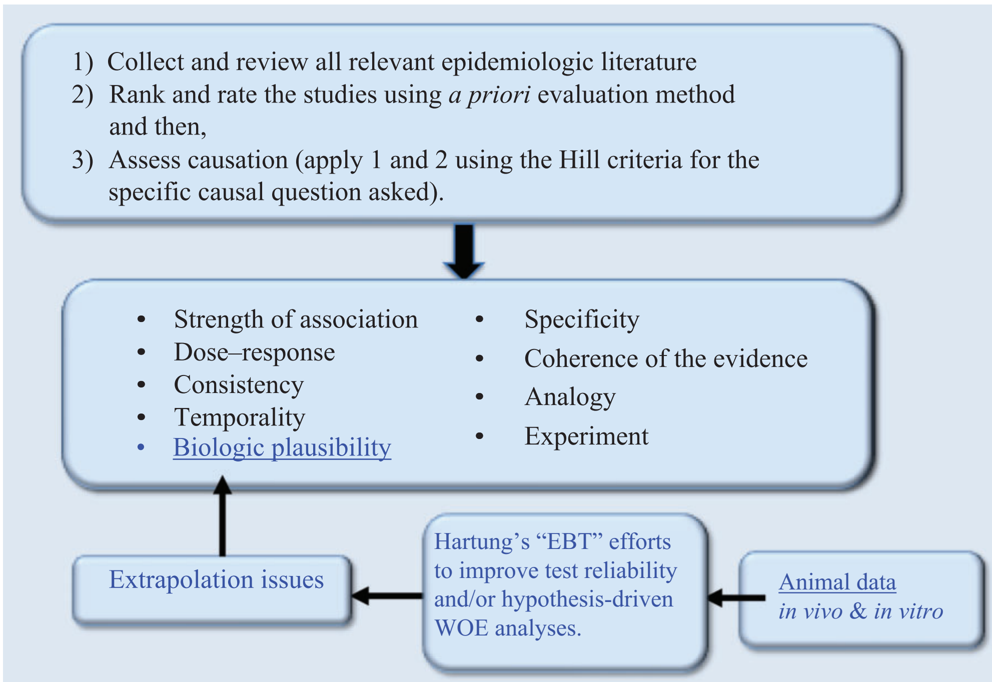

Figure 2. EBT causation logic.
EBT: evidence-based toxicology.

extrapolation to impact other Hill criteria, thereby becoming too pervasive in the overall causal analysis. There are a number of key failures with the application of animal extrapolations that amply illustrate why animal data should be judged cautiously and generally not used as the tipping point to reach a human causation conclusion where the epidemiology evidence is still not sufficient by itself.[23,25,32,33] In particular, the recent tragedy of hormone replacement therapy is a clear evidence that predicting the human outcome via animal data when the epidemiologic evidence is insufficient can produce disastrous outcomes. In an EBT analysis, toxicology provides guidance to epidemiology, as noted above, but qualitative studies of the actual human response provide the final answers regarding human causation.

The terms "risk" or "risk factors" is another area where regulatory agencies have introduced a broader, less specific meaning that differs from the way these terms are used in medicine and epidemiology. The term risk has three components to it: (1) the causal agent (*risk factor*); (2) the adverse effect(s) (*the hazard*); and (3) the probability that exposure to the agent will result in the adverse effect (*the numerical risk*). These are referred to as: (1) the *causal agent component*; (2) the *hazard (adverse effect) component*; and (3) the *probability (dose–response) component*. Examples of an epistemic or real human risk statement are illustrated below:

> There is a 10% risk [*probability component*] of getting lung cancer [*hazard component*] for any person with a 20+ pack-year history of cigarette smoking [*causal agent component*].

Or,

> Statistics have shown that the risk of drowning [*hazard component*] is 1/100,000 [*probability component*] when swimming without a life jacket [*causal agent component*].

In contrast, when causality is not known or knowable because of insufficient human data, and answers from animal data are used to close the data gaps, then an unquantifiable amount of uncertainty is introduced into all three components of the risk statement. This reduces a true human risk statement to a *hypothetical risk statement*. When the causal relationship is not known to be true, both the *causal and hazard components* are missing and are replaced by hypothetical presumptions of unknown certainty. In turn, the probability component is reduced to a *possibility component* because one does not have an actual measure

Figure 3. Acceptance of the evidence-based causation method or its components.[5,10,11,16,31,36–41]

of the true human risk when using animal data. Instead, the true probability has been replaced by another uncertain species extrapolation, and so the numerical estimate provided represents just one nomologic possibility of uncertain accuracy. On this issue, we note that a regulatory agency like the USEPA has long recognized that their "risk assessments" or "risk statements" contain presumed or hypothetical components. For example, regarding the toxicity constants used to generate "USEPA-like risk/uncertainty" estimates provided in its Integrated Risk Information System (IRIS), the USEPA notes what many nonscientists fail to understand about these values, that is, they cannot be used to predict the true incidence of human disease. This is because they are not true measures of the human risk, if it is in fact present.

> In general IRIS values cannot be validly used to accurately predict the incidence of human disease or the type of effects that chemical exposures have on humans. This is due to the numerous uncertainties involved in risk assessment, including those associated with extrapolations from animal data to humans and from high experimental doses to lower environmental exposure. The organs affected and the type of adverse effect resulting from chemical exposure may differ between study animals and humans. In addition, many factors besides exposures to a chemical influence the occurrence and extent of human disease.[34]

Likewise, since 1986, the USEPA has noted that its cancer risk estimates only represent an upper bound estimate of the possible human risk, the true human risk may be a much lower number and in fact may be zero.

These concessions, where the probability component of USEPA risk statements is based on assumed hypotheticals, clearly indicate their use of the term risk is decidedly different from the way this term is applied in epidemiology and medicine. Recognizing that these regulatory risk estimates *are protective but not predictive* is merely a scientific fact that has been conceded

by the agency itself. This feature is something that limits their use but does not undermine their intended purpose, that is, to provide protective exposure guidelines. So, while we have always agreed this approach of using hypothetical presumptions meets the goal of setting health protective exposure guidelines whenever human causation is not knowable, we disagree with calling these uncertain hypothetical characterizations of nomologic possibilities risks. Risk is an epistemic term in medicine, and the regulatory use of nomologic possibilities should more correctly be labeled as such (e.g. "hypothetical risks" or "risk uncertainties" or "nomologic risks") to differentiate possible/nomologic hazards from those epistemic determinations of known risks and risk factors. In fact, it is for this reason the National Academy of Sciences stated there is no regulatory necessity to corroborate human causation for animal-derived carcinogenic or noncarcinogenic hazards, as the USEPA safety/risk assessment is the same, regardless of whether or not human causation is known.[35]

In summary, an understanding of the benefits of applying evidence-based logic to toxicology has improved considerably in the last decade (see Figure 3).

Certain strengths of this methodology, like evidence-based data gathering and review, are now widely adopted in toxicology today. The improvement in medical practice created by EBM is now indisputable; in fact, it has been cited as one of the top 15 milestones in modern medicine.[42] So, on this 10th anniversary, we renew our suggestion that toxicologists likewise adopt evidence-based causation logic when addressing causal issues. EBM/EBT provides an objective and transparent method by which causation is determined, and its use would help eliminate the limitations of regulatory-like WOE analyses similar to those lodged more than a decade ago by Ruden.[29] EBT has always required the systematic collection and review of the literature, a process now widely endorsed in toxicology.[3] Adding an a priori study analysis methodology eliminates the variations created by differing authoritative opinions that might otherwise influence the overall causation analysis, improving the reliability and consistency of the final decision. EBM/EBT requires a transparent and auditable decision-making process guided by the availability of good evidence itself. It recognizes the differences between nomologic and epistemic risks, something that does not adversely impact toxicology or regulatory goals, and it would improve the accuracy of the risk statement being communicated to others by identifying which of the three components were based on epistemic evidence versus an uncertain assumption or extrapolation that represents one of the several nomologic possibilities. We resubmit that such changes enhance the causation analyses of adverse effects and anticipate a further transition toward this goal in the years to come.

Authors' Note

The authors have consulted or testified for parties involved in regulatory and litigation issues where the toxicities caused by chemical exposures were at issue.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Exhibit M

Toxicology: Open Access

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Short Communication Open Access

The Role of Systematic Review in the Practice of Toxicology and Risk Assessment–An Appreciation for the Primary Tool in Evidence-Based Practice

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Abstract

Use of systematic reviews (SRs) as a tool to facilitate evidence-based toxicology (EBT) assessments is increasing, though the field has yet to develop an appreciation of the rigor required to appropriately utilize this tool. Toxicologists should recognize the weight of the term, understanding that a systematic review involves far more than conducting elements of a review systematically. Key aspects that appear to be currently underappreciated include development and publication of a protocol, the level of documentation involved in the conduct of a SR, and the overall level of effort required to maintain standards of SR. As many regulatory agencies and health organizations integrate systematic review into their procedures, it is clear that there is a need to develop best-science practices in EBT, as the methods developed for evidence-based medicine (EBM) do not always provide the best platform for evaluation of toxicological data. Such efforts are particularly needed for evidence integration, methods which allow for integration of multiple types of data, as well as application of the SR in both qualitative and quantitative hazard or risk assessments. Nonetheless, use of systematic review is advancing the field of toxicology, providing objectivity and transparency in evidence-based assessments.

Commentary body

The use of systematic reviews (SRs), which has long-been used in the fields of medicine and other scientific disciplines, as a tool in the field of toxicology is gaining significant interest [1-4]. This tool clearly aids in modernization of evidence-based decision making, though the field as a whole has yet to develop an appreciation of the rigor required to adequately utilize the systematic review as the primary tool in evidence-based toxicology (EBT). By definition, systematic review is a method for answering specific research questions – it uses a predefined, multistep process to identify, select, critically assess, and synthesize evidence from scientific studies to reach a conclusion [5,6]. Many systematic review frameworks exist within the field of evidence-based medicine (EBM) (e.g., IOM, AHRQ, GRADE, PRISMA); however, fewer frameworks and guidance tailored to EBT are available. Though not a comprehensive review, in this commentary, the role of systematic review in toxicology is highlighted, and in doing so, should provide an appreciation for the rigor and resources required to appropriately utilize this tool, as well as the need for continued development of best-science practices in EBT.

Efforts to integrate systematic review in the field of toxicology are substantiated by decades of use of systematic review as a tool in evidence-based medicine (EBM), as highlighted by the existence and operations of large organizations devoted to the systematic assessment of healthcare interventions, such as Cochrane and the Agency for Healthcare Research and Quality (AHRQ). Guzelian et al. were early adopters of the evidence-based vision, issuing a framework for evidence-based toxicology (EBT) in 2005 that was specifically focused on the determination of causation. Since that time, many efforts in the field involving regulatory, academic, non-profit, and private entities have furthered the integration of evidence-based practices into toxicology. For example, in 2011, the National Research Council (NRC) recommended that the U.S. Environmental Protection Agency (USEPA) utilize a consistent, transparent, and systematic approach for the identification, evaluation, and integration of data for assessing hazards to human health [7]; these recommendations were further delineated in 2014 [8]. As a result of such, the Integrated Risk Information System (IRIS) Program is currently in the process of developing and implementing a systematic review process. The USEPA has also issued a draft handbook on the conduct of SRs in the IRIS program and is due to release an updated version imminently.

Other key efforts are highlighted by those from the National Toxicology Program's Office of Health Assessment and Translation (OHAT); in 2012, OHAT began developing an approach for the implementation of SR methodology to carry out literature-based evaluations to reach conclusions about potential health hazards. In 2014, the group published an approach, followed by the issuance of a handbook and RoB tool in early 2015 [9]. The U.S. Food and Drug Administration (FDA)'s [10] Center for Food Safety and Applied Nutrition (CFSAN), which has already been advocating the use of evidence-based review methods [11-13] recently (June, 2015) held a colloquium with the Society of Toxicology regarding SR; topics were based on integration of SR in human health assessments and included problem formulation and scoping, identification and selection of evidence based, harmonizing dose-response, and use of mechanistic data. State and other health organizations in the U.S. are also integrating SR; for example, in November of 2014, the Texas Commission on Environmental Quality (TCEQ) issued a position paper on Recommendations for Systematic Review and Evidence Integration. The International Agency on for Research on Cancer (IARC) is also utilizing elements of systematic review, as highlighted by a recent publication by Smith et al. in which the authors provide ten key characteristics of carcinogens as a basis for organizing data on the mechanisms of carcinogens. Other independent organizational efforts have made significant efforts to provide direction and examples of the

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integration of SR into toxicology, highlighted perhaps by those from, the Navigation Guide, a University of California, San Francisco Program on Reproductive Health and the Environment, as well as the Evidence Based Toxicology Collaboration [14], based out of the Johns Hopkins Bloomberg School of Public Health.

Most systematic review frameworks have common components including: problem formulation and protocol development, identification and evaluation of individual studies, assessment and integration of the body of evidence (qualitatively or quantitatively), and reporting of the SR. Problem formulation and protocol development is a common exercise in the field of EBM, though the rigor and resources needed to conduct this phase appear to be particularly underappreciated in the field of EBT. The early decisions made during protocol development have significant impact on the scope and form of the systematic review, thus underscoring the critical nature of a well-developed approach. The most obvious exercise in problem formulation involves development of objectives and/or hypothesis; in SR, this exercise is carried out via the development of PECO (population, exposure, comparator, and outcome) statements and associated rationale. Not as obvious, however, is the critical nature of well-formulated questions, as they have a significant impact on other components of the review – including the literature search strategy, data extraction, synthesis, and presentation of findings. In practice, formulation of the topic via PECO questions (or statements) is an iterative practice, which is best informed by a multidisciplinary team and considerations for the downstream implementation of the entire SR.

Development of PECO statements is an example of an aspect clearly differentiating SR methods in EBT relative to EBM. In EBM, PICO (population, intervention, comparator, and outcome) statements are utilized. The key difference, exposure versus intervention, is often significantly more difficult to define and standardize in the practice of EBT. Unlike the field of medicine, exposures, particularly to humans, in the field of toxicology are accidental in nature, or occur as part of industrial practices and/or low-level environmental exposures. As such, assessment of exposure in humans will often be complicated relative to that obtained from randomized control trials available in the field of medicine. Other study types (e.g., cohort, case-control, cross sectional) will often be the only source of information in humans. In contrast, assessment of exposure in animal studies is more straightforward, thus often leading toxicologists to a preference for this data type, despite availability of data characterizing potential hazards in humans – a topic which exemplifies the need for a priori approaches for both the critical assessment of individual studies as well as approaches for integrating the data across data streams. And, lastly, assessment of mixtures presents somewhat unique challenges in the practice of EBT; the definition of the mixtures and the definition of exposure to a given mixture can clearly have a significant approach on a SR.

Problem formulation involves additional aspects often not considered in a traditional narrative review. Included in these early exercises should be identification of team members, facilitators, sponsors, etc. as well as specific roles for each person. As established both in SR guidance, and in practice, integration of a multidisciplinary team that includes subject matter experts, as well as experts in systematic review, librarians, and potentially other experts (e.g., epidemiologists, physicians, industrial hygienists) as appropriate to the review. Conflict of interest (COI) statements are also a key component of initiating a review, though implementing standard processes for obtaining and managing COI information does not yet appear to be consistently practiced in the field toxicology. The conduct of pilot endeavors throughout the process should also not be undervalued. Such pilot exercises include: initial literature searches, pilot evaluation of screening criteria (i.e., inclusion and exclusion criteria), processes, and software, as well as pilot application of grading frameworks and/or criteria to the studies of interest. These exercises are crucial to informing the scope and implementation of the protocol and have a direct impact on consistency, efficiency, and transparency, particularly when users adhere to a strict documentation policy.

The best practices for the assessment of individual studies and subsequent integration of evidence are perhaps the topics of greatest research and debate currently in the field of EBT. There are differing opinions regarding the evaluation of the "quality" of individual studies with or without using checklists, scores, or grades versus assessment using more of a qualitative spectrum or continuum. One of the primary issues in developing best practices for individual study assessments is to first clearly define what is meant by study quality in a given SR, given that the parameters of interest to study quality may be dependent on the particular PECO statement of interest. Significant focus has been on assessment of risk of bias (RoB) (i.e., measure of the design and conduct of the study to determine credibility of the link between exposure and outcome; OHAT 2015), and, specifically, frameworks to evaluate RoB in parallel for multiple evidence streams (i.e., human, animal, mechanistic). However, risk of bias itself is not defined consistently, nor is it the only aspect of evaluating study "quality" that is important. Other "quality" aspects of individual studies, such as indirectness (i.e., applicability) and imprecision, are important considerations in determining overall quality and relevance. An appreciation for the rigor and efforts associated with evaluating individual study quality, including RoB, can be emphasized simply by the existence of more than 100 tools for evaluating such. And as a result, appreciation for the forethought and considerations regarding selection of such a framework, or in many cases, frameworks (depending on the scope and intentions of the SR), during problem formulation, cannot be underemphasized.

Similar issues exist with respect to assessment of the body of evidence, and of particular interest in toxicology, integration of multiple types of data, and application of the SR in both qualitative and quantitative hazard or risk assessments. This particular juncture appears to be of greatest need in terms of developing best practices. And foremost, first establishing that the application of the SR has a significant impact on the conduct of such. Unlike the use of SR in clinical medicine to evaluate interventions, SRs are used in toxicology to assess a broader range of outcomes and applications. For example, the outcome may be as broad as characterizing the potential for hazardous or adverse effects, thus requiring accommodation for multiple endpoints (e.g., hepatotoxicity, cardio toxicity, reproductive toxicity) within a single SR. Accordantly, the approach taken, as well as the depth of the assessment, would likely therefore be influenced by the volume of data available.

In other cases, the scope could be very narrow (e.g., specific birth defect observed following exposure to a compound during pregnancy), and the objective could risk-based and include the development of a health-based toxicity value, rather than qualitatively characterizing potential hazard. In such a case, the PECO and subsequent approach would likely be structured differently, with focus on candidate dataset selection and approaches for assessing the data qualitatively. For the later, methods may not involve standard quantitative approaches

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utilized in SRs (i.e., Meta analyses), but rather approaches for conducting dose-response modelling, etc. The application of SR with a risk context also raises additional challenges, ranging from reliance on a specific evidence stream (e.g., animal data from a high-dose carcinogenicity study with controlled exposures versus environmental epidemiological data) to considerations for kinetics and dynamics as well as environmental or consumer exposures (i.e., dose/exposure relevance) – all of which have a significant role in traditional risk assessment. It is thus notable that the NTP's OHAT Handbook for Conducting Systematic review indicates that considerations for ADME and exposure should be made in developing overall hazard conclusions; however, guidance on integration of these parameters is not due to be available until 2016/2017 [9].

Many of these topics have been addressed in a series workshops held by the USEPA IRIS Program [11]. At the recent USEPA workshop on Advancing Systematic Review held in December, 2015, it was evident that the there is significant interest in the application of systematic review in the discipline of toxicology, but that the field remains in its infancy with respect to determining best practices. During the workshop, various case studies were presented, demonstrating the unique nature of each systematic review, as well as the unique nature of an EBT SR versus an EBM SR.

The second day of the workshop focused on assessment and integration of mechanistic data in SR. As an evidence stream that is generally unique to EBT, fewer frameworks and guidance are available. Several presentations at the workshop were focused on a recent publication by Smith et al. [12], in which the authors provided ten key characteristics of carcinogens as a basis for organizing data on the mechanisms of carcinogens. Dr. Guyton, an author on the paper, presented applications of these data and discussed use of the characteristics within IARC evaluations. However, guidance on how these characteristics can be applied beyond organization of data is not yet available. For example, Smith et al. does not provide guidance on how to integrate null findings, how quality/validity and relevance are considered, or how the number of characteristics with positive/negative influences the body of evidence. And, importantly, there is not yet a clear vision on how these characteristics can be applied relative to current practices in the assessment of mode of action for carcinogens, or how they could be used to evaluate high throughput data. There is also not yet a consensus that mechanistic data should be considered a separate stream – rather, should such data be considered contextual. Such a demonstration provides an excellent example of progress in the field of EBT, but also demonstrates the progress yet to be made.

And lastly, perhaps, an area that deserves certain appreciation is the amount of time and resources required conduct a systematic review. With respect to the amount of time, some of the exercises that differentiate the systematic review from a standard narrative review include: development and publication of a protocol, documentation of the literature search (including documentation of all records that were included/excluded), and a critical evaluation of each study using an approach determined a priori. Estimates of time needed to complete problem formulation are highly variable, but are not measured in minutes or hours; pilot screening has been estimates at 1->5 minutes per hit, full screening at 1-2 minutes/hit (plus time for conflict/group review), >2 hours/outcome while piloting individual study assessment, and ~1.5 to 3 hours/outcome (with outliers in both directions) for the bulk of individual study assessments [9,15]. Much of the time estimates are dependent on factors such as the number of collaborators, experience of team with SR processes, number of databases (and associated software compliance), establishment of internal processes and procedures, documentation, grading approaches, number of endpoints and outcomes, as well as overall complexity of the topic under investigation.

Typically, many of the exercises are also carried out by two evidence analysts, and the overall project informed by a multidisciplinary team (including a librarian). Though software programs are available to help facilitate various tasks within a systematic review, the resources and time required to conduct a SR relative to a standard narrative review are significantly greater. As such, there is also a need to balance rigor with efficiency, recognizing that not all SRs will achieve a similar level of detail or comprehensiveness. Key to achieving the balance is selecting tasks with most value added, and, most importantly, providing transparency to the decisions via a priori documentation and rationale.

The use of systematic review is advancing the field of toxicology, providing objectivity and transparency in our practice. The limited number of EBT SR publications relative to EBM highlight the infancy of the integration of this tool in toxicology. As we go forward, we must not haphazardly use the term systematic review, as it clearly bears weight – too often, already, the term is misused, referring only to elements of an exercise that were conducted systematically. We must also continue to move toward determining best practices, and in doing so, develop a greater appreciation for the tool that allows us conduct evidence-based toxicological assessments.

Conflict of interest statement

Dr. Wikoff and Britt report no conflicts of interest; either author or their employer received external funding in developing this commentary.

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Exhibit N

2015 WL 12426834
Only the Westlaw citation is currently available.
United States District Court, W.D.
Missouri, Southwestern Division.

Jodelle L. KIRK, Plaintiff,
v.
SCHAEFFLER GROUP USA, INC., Fag Holding, LLC, and Fag Bearings, LLC, Defendants.

No. 3:13-cv-5032-DGK
|
Signed 09/29/2015

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ORDER DENYING IN PART MOTION TO EXCLUDE DEFENDANTS' EXPERTS

GREG KAYS, CHIEF JUDGE, UNITED STATES DISTRICT JUDGE

***1** This case arises from Defendants' release of trichloroethylene ("TCE") into the environment near Plaintiff Jodelle Kirk's childhood home. Plaintiff alleges she was exposed to this TCE and that it caused her to develop serious medical problems, including autoimmune hepatitis ("AIH").

Now before the Court are Plaintiff's motions to exclude the testimony and opinions of Defendants' experts Dr. Philip Guzelian, M.D. (Doc. 152); James Kline, CPA (Doc. 173); and Dr. B. Tod Delaney, Ph.D., P.E., BCEE (Doc. 175). Also pending are the parties' requests for hearings and oral argument on the motions (Doc. 197). Because the existing record provides a sufficient basis on which the Court can rule, the parties' requests for hearings and oral argument are denied.

For the following reasons, the motions are DENIED with respect to Dr. Guzelian and Mr. Kline's testimony, and GRANTED with respect to Dr. Delaney.

Standard

When the admissibility of expert testimony is challenged, the district court must make "a preliminary determination of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue." *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 592-93 (1993). The party seeking to introduce the expert's testimony bears the burden of establishing its admissibility by a preponderance of the evidence. *Lauzon v. Senco Products, Inc.*, 270 F.3d 681, 686 (8th Cir. 2001). Under Federal Rule of Evidence ("FRE") 702, a witness may give an expert opinion if the following conditions are met:

> (a) the expert's scientific, technical or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; (b) the testimony is based on sufficient facts or data; (c) the testimony is the product of reliable principles and methods; and (d) the expert has reliably applied the principles and methods to the facts of the case.

In other words, the proponent must show that the expert's opinions are relevant, the expert is qualified to offer them, and "the methodology underlying his conclusions is scientifically valid." *Marmo v. Tyson Fresh Meats, Inc.*, 457 F.3d 748, 757-58 (8th Cir. 2006). Doubts should be resolved in favor of admissibility. *Id.* at 758.

Analysis

I. Dr. Guzelian's testimony is admissible under FRE 702.
Dr. Philip S. Guzelian, M.D., is a retired doctor and toxicologist Defendants retained to analyze and rebut the

opinions of Plaintiff's three causation experts, Drs. Kathleen Gilbert, Ph.D., Ernest Chiodo, M.D., and Allen Parmet, M.D. Generally speaking, Dr. Guzelian opines TCE is not known to cause AIH in humans, and that even if it were known to cause AIH in humans, Plaintiff's experts have failed to adequately define a dose that would have been sufficient to cause Plaintiff's AIH. Guzelian Rep. (Doc. 170-19) at 111, 125, 148, 169.

Plaintiff seeks to exclude Dr. Guzelian's testimony, arguing that: (1) he is not qualified to testify whether TCE causes AIH; (2) he did not use a reliable toxicology methodology to reach his conclusions; (3) he misapplied his methodology to the facts of this case; (4) his opinion is unreliable because it was developed for purposes of this litigation. Plaintiff also notes that in 1999, a federal court excluded him from testifying as an expert witness under Rule 702.

***2** The Court is not persuaded by these arguments. First, Dr. Guzelian is qualified to testify whether TCE causes AIH. Although he has no specific expertise in AIH or TCE and has not conducted experiments involving TCE or published any peer-reviewed papers involving TCE, Dr. Guzelian has extensive experience treating liver disease, and he is an accomplished toxicologist with significant academic credentials. Furthermore, it is well-established that a toxicologist may testify that exposure to a chemical caused a person's injuries. *Marmo*, 457 F.3d at 758; *Bonner v. ISP Tech., Inc.*, 259 F.3d 924, 928-31 (8th Cir. 2001). Plaintiff's concerns go to the weight his testimony should receive, not its admissibility.

With respect to Defendants' second argument, it is a close call whether Dr. Guzelian's testimony is the product of a reliable methodology. His methodology used here, "Evidence-Based Toxicology" ("EBT"), posits that only human studies can establish a chemical causes harm to humans. Guzelian Dep. (Doc. 153-1) at 73:8-12. Dr. Guzelian firmly believes animal studies alone can almost never establish causation. *Id.* at 59:17-24. [1]

Toxicologists have recognized EBT's existence, and it has been discussed in toxicological journals, but it is not widely-accepted, much less "widely-cited with approval in the peer-reviewed literature" as Defendants suggest. The concluding sentence of Dr. Guzelian's journal article introducing this methodology acknowledges as much. It states: "It is time for toxicologists to endorse EBT." Philip S. Guzelian, et al., *Evidence-Based Toxicology: A Comprehensive Framework for Causation*, 24 Hum. & Experimental Toxicology 161, 192 (2005) (Doc. 153-2).

The notable characteristic of this methodology is that it makes it more difficult for toxic tort plaintiffs to establish general causation. This is particularly true with respect to substances, like TCE, that cannot ethically or legally be tested on humans. Because animal experiments cannot establish causation, plaintiffs are forced to rely on epidemiological studies or occupational studies. But for rare diseases like AIH, epidemiological studies cannot be effectively done and there are far fewer occupational studies. Thus it is significantly more onerous for plaintiffs to prove their case.

On the other hand, the Court acknowledges that numerous other factors related to his methodology weigh in favor of admitting his testimony. Dr. Guzelian is well-qualified, and his report applies nine well-established guidelines, commonly known as the Bradford Hill criteria, to analyze whether TCE has been shown to cause AIH in humans. *See In re Neurontin Mktg., Sales Practices, & Prods. Liab. Litig.*, 612 F. Supp. 2d 116, 132-33 (D. Mass. 2009) (observing courts have generally accepted the Bradford Hill criteria). Additionally, in formulating his opinions, Dr. Guzelian carefully reviewed and analyzed the expert opinions he is critiquing, and he reviewed exhaustively the published human and animal studies. Hence, his testimony is based on facts and data.

Dr. Guzelian has also published two peer-reviewed articles on EBT methodology. His first paper has been cited in other publications at least seventy-eight times. In fact, it is the sixth most cited article in the thirty-five year history of the journal Human & Experimental Toxicology, which *The Reference Manual on Scientific Evidence* acknowledges is a "reputable, peer-reviewed journal." Bernard Goldstein & Mary Sue Henifin, *Reference Guide on Toxicology, in Reference Manual on Scientific Evidence*, 633, 678 (Fed. Judicial Ctr. ed., 3d ed. 2011). In sum, the Court cannot say that his methodology is "fundamentally unsupported" and should be excluded. *Bonner*, 259 F.3d at 929-30 (holding an expert's testimony should be admitted unless the opinion is so fundamentally unsupported that it can offer no assistance to the jury); *see Synergetics, Inc., v. Hurst*, 477 F.3d 949, 956 (8th Cir. 2007) ("[M]ere disagreement with the assumptions and methodology used does not warrant exclusion of expert testimony."). The Court is also mindful that doubts should be resolved in favor of admissibility. *Marmo*, 457 F.3d at 758.

*3 The Court finds no merit to Plaintiff's third argument that Dr. Guzelian did not correctly apply his methodology to the facts of this case. Plaintiff argues that if he had, he would have concluded a cause and effect relationship exists between TCE and autoimmune disease. For support, Plaintiff quotes the Environmental Protection Agency's ("EPA") 2011 *Toxicological Review of Trichloroethylene*, which summarizes the results of various studies. In relevant part, it states, "The human and animal studies of TCE and immune-related effects provide *strong evidence* for *a role* of TCE in *autoimmune disease*." Weihsueh A. Chiu, et al., *Toxicological Review of Trichloroethylene*, U.S. EPA (2011), *full text available at* http://www.epa.gov/iris/toxreviews/0199tr/0199tr.pdf, at 4-427.

This argument is not persuasive. As a threshold matter, Plaintiff exaggerates the strength of the EPA review's conclusion. The review concludes that human studies provide *strong evidence* that TCE plays *a role* in autoimmune disease, not that human studies *show* TCE *causes* autoimmune disease. Indeed, it is unclear whether the review's conclusion and Dr. Guzelian's position are incompatible with each other. The EPA review concludes there is a relationship between TCE and autoimmune disease generally, while Dr. Guzelian's position is that no studies have established a causal relationship between TCE and AIH in humans. Although a correlation between TCE and autoimmune disease makes it more likely that a causal relationship exists between TCE and AIH in humans, this does not mean Dr. Guzelian's conclusion is somehow inconsistent with the EPA's conclusion. Hence, the Court cannot say Dr. Guzelian's report fails to apply his own methodology.

With respect to Plaintiff's fourth argument, the Court holds Dr. Guzelian's opinions should not be excluded as unreliable even though they were "developed for litigation." Dr. Guzelian's opinion cannot be excluded simply because he has not previously opined, outside of this case, whether TCE has been shown to cause AIH in humans. If that were the standard, several of Plaintiff's experts would be prohibited from testifying as well, because they did not develop their opinions independently of this lawsuit. The question is whether Dr. Guzelian's "*expertise* was developed for litigation or naturally flowed from the expert's research." *Lauzon*, 270 F.3d at 687 (emphasis added).

Furthermore, this factor is only one of many to consider in determining the admissibility of Dr. Guzelian's opinion. *See id.* Other relevant factors, such as whether he "ruled out other alternative explanations" and "sufficiently connected the proposed testimony with the facts of the case," weigh against excluding his testimony.

Finally, the fact that Dr. Guzelian was previously excluded from testifying as an expert witness is not relevant because that case is not analogous to this one. The issue in the 1999 case was whether there was an accepted, effective treatment for a Tegretol overdose, a question far afield of his expertise. Furthermore, the court's decision to exclude Dr. Guzelian appears to have been determined as much by the proponent's failure to submit a well-researched brief as by any perceived lack of expertise. *Harvey v. Rines*, No. 98-85-P-DMC, 1999 WL 33117105, at *6 (D. Me. Jan. 19, 1999) (noting the response defending the admissibility of his testimony failed to cite any "authority or the record").

Although it is a close call, the Court holds Defendants have established the admissibility of his testimony.

II. James Kline's testimony is admissible under FRE 702.

James Kline is a certified public accountant ("CPA") employed by McGladrey. Defendants retained him to offer a rebuttal opinion on Dr. Ward's report of economic damages and the underlying data on which his report rests. Mr. Kline has provided testimony concerning the calculation of damages in over twenty cases, four of which involved the calculation of lost earnings. He opines that Dr. Ward's report "contains errors, deficiencies, inconsistencies, and unsupported assumptions that result in an overstatement of estimated damages," thus its conclusions are "flawed and do not provide a reliable estimate of the economic damages in this matter." Kline Rep. (Doc. 170-24) at 5.

*4 Plaintiff moves to exclude Mr. Kline's testimony, arguing he is not qualified to rebut any opinion by Dr. Ward, Kathie Allison (Plaintiff's certified life care planner), or Terry Cordray (Plaintiff's vocational rehabilitation specialist). In response, Defendants note Mr. Kline is highly qualified to rebut Dr. Ward's opinions. They also observe that Mr. Kline's report mentions Ms. Allison's and Ms. Cordray's opinions only to rebut Mr. Ward's calculations and conclusions, and to show that he relied on obviously flawed information.

The Court rules as follows. Plaintiff's contention that as a matter of law CPAs lack the education and experience to testify on economic damages is patently incorrect. Courts

routinely admit the testimony and opinions of CPA on various issues of economic loss and damages. *See, e.g., Johnson v. Cowell Steel Structures, Inc.*, 991 F.2d 474, 477 (8th Cir. 1993) (admitting testimony from two CPAs on economic damages issues such as business interruption, business valuation, and projected loss and cash flow); *Tipton v. Mill Creek Gravel, Inc.*, No. 01-5027-CV-SW-JCE, 2003 WL 25686521, at *1-2 (W.D. Mo. May 2, 2003) (allowing CPA to testify on economic damages issues such as the net value of gravel and anticipated expenses). Accordingly, Defendants have established that Mr. Kline's testimony is admissible.

III. Dr. Delaney's is excluded from offering any testimony in his expert report responding to "Plaintiff's Opinion 1."

Dr. B. Tod Delaney is an engineer retained by Defendants to rebut opinions proffered by Plaintiff's expert witnesses Drs. Everett and Wells. Plaintiff moves to exclude Dr. Delaney from offering any testimony rebutting the doctors' first opinion, which was that Defendant FAG Bearings released large quantities of toxic chemicals, including TCE, into the environment at its Joplin facility. Plaintiff argues Dr. Delaney's testimony violates a Court ruling holding Defendants are barred by the doctrine of collateral estopped from contesting certain allegations. Defendants' response, filed before the Court issued its second order, asserts Dr. Delaney's testimony is not barred.

The Court's June 15, 2015, Order Partially Granting Plaintiff's Second Motion on Collateral Estoppel (Doc. 232) found that collateral estoppel prevents Defendants from litigating thirteen different facts in this case. These include:

* Defendant FAG Bearings released approximately 12,000 to 25,000 gallons of TCE through waste, spills, leaks, overflowing tanks, incidental use of TCE, and dumping of "still bottoms" into the ground at FAG Bearings' facility.

* Defendant FAG Bearings' employees occasionally dumped or pumped TCE directly into the ground. The highest levels of TCE contamination were found at or near these locations.

* Defendant FAG Bearings could not account for approximately 30,000 gallons of TCE it purchased.

* Defendant FAG Bearings' vapor recovery system frequently and repeatedly malfunctioned, releasing large amounts of TCE into the air over a long period of time.

* Defendant FAG Bearings' own experts and employees have opined that these vapors then condensed and returned to the soil on Defendant FAG's property.

* The releases of TCE on Defendant FAG Bearings' property were predictable and foreseeable.

The most significant portions of Dr. Delaney's testimony, however, contradict these facts. For example, he opines that: the TCE released into the environment from the steam condensate system at the Joplin facility "was likely no more than ... 1,200 – 3,900 gallons;" "FAG's environmental controls and the chemical and physical properties of TCE minimized the amount of TCE that entered the subsurface environment and acted to divert most of the TCE used at the facility into the air;" and that "although the FAG facility used TCE in its operations and released TCE to the environment, it did not release 'large' quantities of TCE into the subsurface environment as claimed by the Plaintiff." Delaney Rep. (Doc. 176-1) at 18-19. The Court finds this testimony is explicitly barred by the Court's June 15 Order, so Dr. Delaney should not be permitted to give it.

*5 Accordingly, Plaintiff's motion is GRANTED. The Court excludes Dr. Delaney from offering any testimony responding to "Plaintiff's Opinion 1" set forth on pages seventeen through nineteen of his expert report. His testimony is limited to rebutting Drs. Everett and Wells' "Opinion 3" as described in pages nineteen and twenty of his report.

Conclusion

For the reasons above, Plaintiff's motions are DENIED with respect to Dr. Guzelian and Mr. Kline's testimony (Docs. 152, 173), and GRANTED with respect to Dr. Delaney's testimony (Doc. 175).

IT IS SO ORDERED.

Date: September 29, 2015.

All Citations

Not Reported in Fed. Supp., 2015 WL 12426834

Footnotes

1 Defendants intimate that Dr. Guzelian's view is akin to that articulated by the Supreme Court in *General Electric Co. v. Joiner*, 522 U.S. 136 (1997). This is simply not true. In *Joiner*, the Supreme Court did not even question whether animal studies alone can be a proper foundation for an expert's opinion on causation; it was a given. *Id.* at 144. Dr. Guzelian, on the other hand, opines that animal studies alone can virtually never establish causation.

End of Document

Exhibit O

2006 WL 166452
Only the Westlaw citation is currently available.
NOT FOR PUBLICATION
United States District Court, D. New Jersey.

Jeff PLAYER, et al., Plaintiffs,
v.
MOTIVA ENTERPRISES LLC, a successor in interest to Star Enterprises, Defendant.

No. Civ. 02–3216(RBK).
|
Jan. 20, 2006.

Attorneys and Law Firms

Keith A. McKenna, McKenna, Mulcahy & McKenna, Montclair, NJ, for Plaintiffs.

Jeffrey W. Moryan, Connell Foley LLP, Roseland, NJ, for Defendant.

OPINION

KUGLER, United States District Judge:

***1** This matter comes before the Court upon motions by Defendant Motiva Enterprises, LLC, ("Defendant" or "Motiva") for summary judgment of the claims of Plaintiffs Jeff Player, et al. ("Plaintiffs"), and to exclude Plaintiffs' experts Michael Gochfeld, M.D., Ph.D. ("Gochfeld"), R. Brian Ellwood, Ph.D. ("Ellwood"), Bruce M. Gallo ("Gallo"), and Daniel McDonald ("McDonald"). For the reasons set forth below, Defendant's motions will be granted in part and denied in part.

I. Background [1]

This environmental contamination suit is brought by the current and former owners of twenty-seven parcels of residential property located in the Spring Hollow Subdivision in Gloucester Township, New Jersey. [2] Plaintiffs allege that emissions from Defendant's nearby Texaco gasoline service station contaminated their property and the Kirkwood Cohansey Aquifer, the underground water source for their potable wells.

Contamination of the aquifer was first detected on April 5, 2000, when significant concentrations of the gasoline-related compound methyl tertiary butyl ether ("MTBE") was discovered in a drinking fountain at Camden County Community College. New Jersey Consumers Water Company ("Consumers"), the entity responsible for providing water to the college, conducted sampling of some of its wells and discovered significant amounts of gasoline-related compounds in municipal supply well number 8 ("CW–8"). Consumers took the well offline on April 10.

While investigating the contamination, the New Jersey Department of Environmental Protection ("NJDEP") detected a discharge of volatile organic compounds ("VOCs") from Defendant's service station, located at 585 Berlin Cross Keys Road ("Motiva site" or "contamination site"). [3] The NJDEP issued a Field Directive on April 12, 2000, requiring Motiva to investigate the source and extent of the discharge, to implement an interim treatment system, and to submit a remedial action work plan to the NJDEP. Defendant installed an interim recovery system and twenty-five monitoring and recovery wells between April and June 2000.

The NJDEP issued a second directive on May 5, 2000, ordering Defendant to cease gasoline retail operations and provide treatment or an alternate source of water to replace CW–8. Defendant replaced the interim system with a permanent ground water recovery and treatment system in June 2000, and installed forty-one additional monitoring wells from June 2000 to present. As further required by the NJDEP, Defendant regularly sampled potable wells located on approximately forty residential properties in the vicinity of the Motiva site. Defendant detected small amounts of MTBE in thirteen of the residential wells it sampled. [4]

Per the NJDEP directive, Motiva submitted a Remedial Investigation Work Plan/Remedial Investigation report on July 2000 and a Remedial Action Workplan ("RAW") on November 14, 2000. In its RAW, Defendant requested permission to cease sampling of the residential wells, contending that the MTBE detected in those wells could not have come from the Motiva site since the wells are located upgradient [5] or sidegradient from the site, and no emissions were detected in most of the monitoring wells between the Motiva site and the potable wells. [6] Motiva also claimed that recent literature indicated that traces of MTBE in groundwater could likely result from "non-point sources." (March 2001 Directive at 2.)

*2 Plaintiffs' expert, R. Brian Ellwood, Ph.D ("Ellwood"), submitted a response to the RAW on January 17, 2001. In his report, Ellwood notes that as of January 17, 2001, "[c]ontrol of contamination at depth beneath the site, control of offsite contamination, and possibly control of contamination at the northern site boundary, has not been established." (Preliminary Report Sicklerville Road Groundwater Contamination ("Ellwood Report"), McKenna Cert. in Opp. to Def.'s Mot. Summ. J., filed Oct. 12, 2005 ("McKenna Cert."), Ex. F, at 2.) Ellwood also offered possible theories to demonstrate the plausibility of Defendant's responsibility for the MTBE in spite of Motiva's arguments to the contrary.

The NJDEP ultimately rejected Defendant's request to cease sampling of the residential wells in its March 2001 Directive on the basis that "there is insufficient evidence for Equiva to conclude that the MTBE detected in the 13 potable wells in the area did not originate from the Cross Keys Texaco site" and "that regardless of the source of the MTBE in these wells, which is obviously debatable, ongoing sampling of these wells is required *primarily due to their proximity to the site.*" (March 2001 Directive at 2) (emphasis in original).

Also in the March 2001 Directive, the NJDEP approved a Classification Exemption Area ("CEA") for the site that excluded all but 1/10 of an acre of 583 Berlin Cross Keys Road (the Wallace Property). The CEA establishes the boundaries of a ground water plume where VOCs exceed the GWQS. [7]

Through summer 2004, the NJDEP regularly reduced the testing requirements. By August 18, 2003, the NJDEP required only:

> annual sampling of the wells at 4, 7, 11, 13 and 14 Donna Marie Court; 2, 4, 6, and 8 Latham Way; 12 and 20 Spring Hollow Drive, and; 937 and 948 Sicklerville Road. For all the sampling events of the aforementioned potable wells conducted April 2002, the Department notes that all wells continue to exhibit no gasoline related contamination in excess of the Department's Drinking Water Quality Standards.

(NJDEP Directive, Aug. 18, 2003, McKenna Cert., Ex. D.)

The NJDEP approved shut down of the recovery and treatment system on April 30, 2004. (NJDEP Correspondence, Aug. 9, 2004, Mairo Cert., Ex. S., at 2.) Finally, on August 9, 2004, the NJDEP determined that "Defendant's Remedial Action Progress Reports "meet the conditions of the March 21, 2001 Remedial Action Workplan (RAW) approval. Shell Oil Products U.S. (Shell OPUS) is, therefore, in compliance with N.J.A.C. 7:14B–6." (Aug. 9, 2004, NJDEP Correspondence, Mairo Cert., Ex. S., at 1.)

B. The Residential Properties

Plaintiffs own twenty-seven respective residential properties near Defendant's gasoline station. [8] Twenty-six of the twenty-seven properties-all but 583 Berlin Cross Keys Road ("the Wallace property")-contain potable wells located in the Kirkwood Cohansey Aquifer. Because Plaintiffs' properties are north/northeast of the contamination site, (Undisputed Facts ¶ 38), they are considered upgradient or sidegradient of the contamination site, depending on whether CW–8 is pumping. [9]

*3 Consistent with the requirements of the NJDEP directives, Defendant tested the Plaintiffs' residential wells for six gasoline-related compounds: benzene, toluene, ethylbenzene, xylenes, MTBE, and TBA. No testing detected any gasoline-related compound on eighteen of the properties. [10] Detection of compounds on the remaining eight properties was as follows:

- A single detection of 0.79 ppb toluene and ten detections of MTBE (highest at 15.5 ppb) at 4 Latham Way,
- Three detections of MTBE (highest at 0.76 ppb) at 14 Donna Marie Court,
- Three detections of MTBE (highest at 1.4 ppb) at 6 Latham Way,
- A single detection of 1.4 ppb toluene at 850 Sicklerville Road,

- A single detection of 0.4 ppb MTBE at 4 Donna Marie Court,
- A single detection of 0.3 ppb MTBE at 12 Donna Marie Court,
- A single detection of 1.2 ppb MTBE at 8 Latham Way, and
- A single detection of 0.3 ppb MTBE at 20 Spring Hollow Road.

The GWQS for toluene is 1,000 ppb and the GWQS for MTBE is 70 ppb. No gasoline-related compound was detected on any Plaintiff's property after April 2001.

According to the Certification of Julian Davies, a Project Manager for EnviroTrac, Ltd., an environmental consulting firm retained by Defendant to remediate the Motiva site, the NJDEP never restricted the consumption of water from Plaintiffs' potable wells, and never required Defendant to treat the water, provide Plaintiffs with an alternate source of water, or collect soil samples from the residential properties. [11] (Julian Davies Cert., Mairo Cert., Ex. R, at 2.)

Since the fact of the contamination became known, several Plaintiffs have sold their property. Maria and John Wallace sold 583 Berlin Cross Keys Road for $350,000.00 in September 2001, Plaintiffs Thomas and Tina Stankiewicz sold 9 Spring Hollow Drive in July 2002 for $143,000.00, Barbara Tanner sold 17 Spring Hollow Drive for $134,000.000 in February 2002, Daniel and Maria Rodriguez sold 18 Spring Hollow Drive for $138,000.00 in July 2003, David Lodi sold 5 Donna Marie Court for $104,000.00 in September 2001, 13 Donna Marie Court was sold for $109,900.00 in July 2000, and 19 Spring Hollow Drive was sold for $133,900.00 in May 2001.

Defendant filed motions for summary judgment and to exclude experts on June 24, 2005, after requesting and receiving permission from this Court to extend by one week the date for the filing of dispositive and *in limine* motions. Briefs in opposition were due July 22, 2005, however, Plaintiffs instead filed an untimely request for an extension on August 2, 2005, and a second request on September 6, 2005, moving the deadline to September 30, 2005. On October 5, 2005, Plaintiffs filed another untimely request for an extension, and ultimately did not submit a complete Opposition until October 14, 2005. Nevertheless, because a district court should not grant a motion for summary judgment without examining the merits, *Stackhouse v. Mazurkiewicz,* 951 F.2d 29, 30 (3d Cir.1991) (citing *Anchorage Assoc. v. Virgin Islands Bd. of Tax Rev.,* 922 F.2d 168 (3d Cir.1990)), this Court will exercise its discretion to consider Plaintiffs' Opposition, even though it is untimely. Local Civ. R. 7.1(d)(5).

II. Standard

***4** Summary judgment is appropriate where the Court is satisfied that "there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed.R.Civ.P. 56(c); *Celotex Corp. v. Catrett,* 477 U.S. 317, 330, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986). A genuine issue of material fact exists only if "the evidence is such that a reasonable jury could find for the nonmoving party." *Anderson v. Liberty Lobby, Inc.,* 477 U.S. 242, 248, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986).

The burden of establishing the nonexistence of a "genuine issue" is on the party moving for summary judgment. *Celotex,* 477 U.S. at 330. The moving party may satisfy this burden by either (1) submitting affirmative evidence that negates an essential element of the nonmoving party's claim; or (2) demonstrating to the Court that the nonmoving party's evidence is insufficient to establish an essential element of the nonmoving party's case. *Id.* at 331.

Once the moving party satisfies this initial burden, the nonmoving party "must set forth specific facts showing that there is a genuine issue for trial." Fed.R.Civ.P. 56(e). To do so, the nonmoving party must "do more than simply show that there is some metaphysical doubt as to material facts." *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.,* 475 U.S. 574, 586, 106 S.Ct. 1348, 89 L.Ed.2d 538 (1986). Rather, to survive summary judgment, the nonmoving party must "make a showing sufficient to establish the existence of [every] element essential to that party's case, and on which that party will bear the burden of proof at trial." *Serbin,* 96 F.3d at 69 n. 2 (quoting *Celotex,* 477 U.S. at 322); *Heffron v. Adamar of N.J., Inc.,* 270 F.Supp.2d 562, 568–69 (D.N.J.2003). "If the non-movant's evidence on any essential element of the claims asserted is merely 'colorable' or is 'not significantly probative,' the court must enter summary judgment in favor of the moving party."

Heffron, 270 F.Supp.2d at 69 (citing *Anderson,* 477 U.S. at 249–50).

III. Motion to Exclude Expert Daniel McDonald

Defendant moves to exclude the testimony of Plaintiffs' expert Daniel McDonald ("McDonald") on the grounds that he is unqualified and his report is unreliable. [12] Admissibility of expert testimony is governed by Federal Rule of Evidence 702 and the United States Supreme Court's decision in *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). [13] In the Third Circuit, the admissibility of expert testimony is contingent on the "qualifications" of the expert and the "reliability" of his methodology. *In re Paoli R.R. Yard PCB Litig.,* 35 F.3d 717 (3d Cir.1994) (interpreting *Daubert*); *see also Oddi v. Ford Motor Co.,* 234 F.3d 136, 145 (3d Cir.2000).

A. *In Limine* Hearing

In certain instances, courts are obligated to provide *in limine* hearings before applying *Daubert* to exclude expert testimony. *Padillas v. Stork–Gamco, Inc.,* 186 F.3d 412 (3d Cir.1999). A hearing is required, for example, where the court excludes an expert's conclusions on the grounds that they are "insufficiently explained and the reasons and foundations for them inadequately and perhaps confusingly explicated." *Id.* In other words, where a report is "conclusory and did not adequately explain the basis for [the expert's] opinion or the methodology employed in reaching his conclusions," the "plaintiff needs an 'opportunity to be heard' on the critical issues of scientific reliability and validity." *Oddi,* 234 F.3d 136, 152 (3d Cir.2000) (holding that the district court did not err "in granting summary judgment here without an *in limine* hearing") (quoting *Padillas,* 186 F.3d at 417). Where the evidentiary record is substantial, however, or the court has before it the information necessary to determine that the expert lacks "good grounds" for his conclusions, an *in limine* hearing may be unnecessary. *Id.* at 153.

***5** The evidence before this Court clearly establishes the process by which McDonald "arrived at his conclusions," *Oddi,* 234 F.3d at 152, and McDonald's report and deposition details the methodology underlying his determinations. As discussed below, this Court will exclude McDonald's testimony on the grounds that his analysis and methodology are baseless and inconclusive, not because his report is insufficiently explained. Additionally, Defendant's motion for summary judgment alerted Plaintiffs to the *Daubert* challenge, yet Plaintiffs neither requested a hearing nor offered any affidavit or evidence in support of McDonald. Accordingly, an *in limine* hearing is unnecessary.

B. Qualifications

The Third Circuit instructs courts to "liberally" evaluate an expert's qualifications. *Oddi v. Ford Motor Co.,* 234 F.3d 136, 145 (3d Cir.2000). In particular, the Circuit has "eschewed overly rigorous requirements of expertise and [has] been satisfied with more generalized qualifications." *In re Paoli,* 35 F.3d at 741 (citing *Hammond v. International Harvester Co.,* 691 F.2d 646, 652–53 (3d Cir.1982) and *Knight v. Otis Elevator Co.,* 596 F.2d 84, 87–88 (3d Cir.1979)). This liberal treatment extends to the expert's substantive qualifications as well as his formal qualifications. *Id.*

Nevertheless, the Third Circuit has "also set a floor with respect to an expert witness's qualifications." *Elcock v. Kmart Corp.,* 233 F.3d 734, 742 (3d Cir.2000). To demonstrate when an expert would not be qualified under Rule 702, the *Elcock* Court offered the pre-*Daubert* case, *Aloe Coal Co. v. Clark Equip. Co.,* 816 F.2d 110 (3d Cir.1987), which held a tractor salesperson unqualified to testify as an expert about the cause of a tractor fire. *Elcock,* 233 F.3d at 742 (citing *Aloe Coal,* 816 F.2d 110).

In *Elcock* itself, the Court determined with "misgivings" that the district court had not abused its discretion by concluding that a psychologist with experience in obtaining employment for disabled individuals was qualified to testify to the possibility for vocational rehabilitation of the injured plaintiff. However, the Court acknowledged that it also would have upheld a decision to exclude the expert since "he seems most qualified to testify on a micro-level regarding the ability of a disabled individual to return to a specific job; he does not appear particularly qualified to testify on the macro-level regarding the number of jobs in the national or local economy that the disabled individual is able to perform." [14] *Elcock,* 233 F.3d at 744. Taken together, *Elcock* and *Aloe Coal* indicate that where a proposed expert's area of experience is

adjacent to, but not actually encompassing, the subject matter of his testimony, he may be deemed unqualified.

McDonald has worked as a licensed appraiser in New Jersey for approximately twenty-two years. Defendant argues that McDonald is nevertheless unqualified to testify to the diminution in value of Plaintiffs' properties because McDonald has no experience in appraising contaminated property. Defendant notes that McDonald has never appraised property allegedly contaminated by emissions from a gasoline station and has never acted as an expert in a situation involving contamination of the groundwater or allegations of a leaking underground storage tank. (Daniel McDonald Dep. ("McDonald Dep."), Mairo Cert. in Supp. Def.'s Mot. to Exclude Plaintiffs' Expert Daniel McDonald, Ex. C, at 23–24.) Defendant also points out that McDonald did not entirely understand the Ellwood and Gallo reports upon which he relied, including the charts indicating the presence and degree of contaminating agents on the property. (McDonald Dep. at 55–56.)

*6 This case lies squarely between *Aloe Coal* and *Elcock.* Although McDonald is an experienced appraiser, no evidence indicates that he has any experience appraising contaminated properties or is qualified to value the effects of stigma on property values. Just as a psychologist experienced in assisting individuals to find work may be unqualified to testify about the general availability of jobs in the economy, an individual able to appraise an uncontaminated property may have no grounds for appreciating the devaluation of the same property under unique conditions of contamination or stigma. Because nothing in McDonald's experience indicates knowledge or expertise in issues of contamination, he is unqualified to testify to the loss of value to Plaintiffs' properties arising from the alleged contamination.

C. Reliability

Because expert testimony has the potential to bear considerable weight with a jury, the district court functions as a gatekeeper responsible for assuring "that the scientific methodology upon which the expert opinion is founded is reliable" and that "the expert's conclusion is based on good grounds." *In re Paoli,* 35 F.3d at 732–33. To ascertain "reliability," the court must examine a number of factors, both those established in *Daubert* and those previously enumerated by the Third Circuit in *United States v. Downing,* 753 F.2d 1224 (3d Cir.1985). *Oddi,* 234 F.3d 145 (citing *Paoli II,* 35 F.3d at 742). In particular, the court must consider:

> (1) whether a method consists of a testable hypothesis; (2) whether the method has been subjected to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put.

Paoli II, 35 F.3d at 742 n. 8; *see also* *Elcock,* 233 F.3d at 746 (noting that "each factor need not be applied in every case"). The party wishing to introduce the testimony bears the burden of establishing "by a preponderance of the evidence that their opinions are reliable." *Paoli,* 35 F.3d at 744.

Of course, an expert's opinion need not be "perfect," and judges may not substitute their opinions for those of an expert. *Paoli,* 35 F.3d at 744; *see also* *Crowley v. Chait,* 322 F.Supp.2d 530, 536 (D.N.J.2004). However, courts also need not admit mere conclusions or "opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *Magistrini v. One Hour Martinizing Dry Cleaning,* 180 F.Supp.2d 584, 608 (D.N.J.2002) (quoting *General Elec. Co. v. Joiner,* 522 U.S. 136, 145–46, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997)).

*7 Mere assumptions, without causal evidence or methodological analysis may be inadmissible. *In re TMI Litig.,* 193 F.3d 613, 667–68 (3d Cir.1999). Conclusions based only on the expert's experience, *Oddi,* 234 F.3d at 140–41, and testimony founded on methods that are not

generally accepted or lack testable hypotheses may also fail to surmount the *Daubert* standard, *Elcock,* 233 F.3d at 746. Furthermore, conclusions based on analogies that are too dissimilar to the subject of the testimony may also merit exclusion. *General Elec.,* 522 U.S. at 144 (rejecting expert testimony that plaintiff's cancer was due to exposure to PCBs when the testimony was based on animal studies of infant mice that had developed cancer after exposure to PCBs).

In response to Defendant's motion to exclude McDonald's testimony, Plaintiffs argue that "Mr. McDonald's opinions are based upon credible facts, NJDEP records, the reports of Plaintiffs' liability experts and individual appraisal reports prepared for each residential property." (Pl.s' Opp. Def.'s Mot. Summ. J. ("Opp."), filed Oct. 12, 2005, at 30.) However, McDonald testified in his deposition that he relied only on the Gallo and Ellwood Reports, and he specifically testifies that he did *not* "review any correspondence from the NJDEP related to this site." (McDonald Dep. at 15.) [15]

In spite of Plaintiffs' arguments to the contrary, this Court cannot avoid the conclusion that McDonald's methodology is entirely unreliable. In his report, McDonald determines that the value of Plaintiffs' properties with no evidence of contamination should be discounted 35% percent and property with onsite contamination should be discounted by 66%. (McDonald Report ("McDonald Report"), Mairo Cert. in Support of Def.'s Mot. Exclude Pl.s' Expert Daniel McDonald, Ex. B., at 31, 33.) McDonald reached the 35% and 66% figures without discussing, or even recognizing, the extent to which the property was actually contaminated. As demonstrated by his ignorance of the "ND"/Not Detected signifier in the Gallo and Ellwood Reports, McDonald did not know how to read the charts denoting the levels of contamination. (McDonald Dep. at 56.) Nor had McDonald ever conducted any physical inspection of or visit to the properties prior to writing the report. [16] (McDonald Dep. at 15–16.)

Furthermore, to quantify the stigma attached to Plaintiffs' properties, McDonald relies upon a highly misleading analogy with a site of profoundly contaminated residential properties in Dover Township. (McDonald Report at 27.) Specifically, McDonald compares Plaintiffs' properties with "an area of Dover Township that had ground water contamination from Union Carbide and ... Ciba Geigy that resulted in what was commonly known as a cancer cluster among children," meaning "an inordinate number of children with cancer." (McDonald Dep. at 158–59.) McDonald selected the Dover site not because of its comparability, but because McDonald "didn't know of any other cases that, where the data was as readily available." (McDonald Dep. at 159.)

***8** Employing the Dover analogy, McDonald determined that the property in the Dover site is in the final stages of recovery and continues to suffer a stigma loss of 13%. Because McDonald considered Plaintiffs' properties in the early stages of recovery, McDonald determined that they must bear a stigma discount of at least two or three times that of the Dover site, resulting in a discount of 35%. [17] However, the severity of the contamination and resulting illness among Dover residents undercuts any grounds for comparison with Plaintiffs' properties where there were few detections of contaminants and no reported physiological effects.

The methodology employed to reach the 66% figure is equally unreliable. To assess the value of properties with some evidence of contamination, McDonald sent an email to thirteen financial lenders to determine whether they would "lend on a property that has known contamination, or the stigma of contamination, to the ground water." (McDonald Report at 32.) Of the thirteen lenders, six replied. One of those refused to comment, and one said that it would loan given certain circumstances. The other four lenders stated that they would not lend on a property that is contaminated, but the content of their brief responses suggested that they understood the email hypothetical to denote property that was actually contaminated and out of compliance with state requirements. [18]

From the results of the email test, McDonald concludes that there would be no buyers other than those who could pay cash. [19] McDonald then assessed the discount in value given cash-only buyers, extrapolating from this a discount of 66%. (McDonald Report at 33.) However, the reliability of the 66% figure is entirely invalidated by the overemphasis placed on the four responses to the email hypothetical, the misleading implication in the email hypothetical, suggesting a much greater contamination of the property than actually present, and the unclear calculations and assumptions underlying McDonald's arrival at 66%.

Ultimately, McDonald's report does not fulfil any of the reliability factors. His method is untestable and arbitrary, without a generally accepted, established, or peer reviewed methodology, and his evaluation was conducted without any

real standards. Because McDonald is unqualified and his evaluation is unreliable, Defendant's motion *in limine* to exclude his testimony will be granted.

IV. Plaintiffs' Claims

A. Negligence and Gross Negligence

To surmount a motion for summary judgment of a negligence claim, Plaintiffs must provide evidence such that a reasonable jury could find "breach of a duty of care and actual damages sustained as a proximate cause of the breach." *Muise v. GPU, Inc.*, 371 N.J.Super. 13, 35, 851 A.2d 799 (App.Div.2004) (citing *Weinberg v. Dinger*, 106 N.J. 469, 484, 524 A.2d 366 (1987)); *Nappe v. Anschelewitz, Barr, Ansell & Bonello*, 97 N.J. 37, 45, 477 A.2d 1224 (1984) ("[T]he plaintiff must show a breach of duty and resulting damage to prevail in a negligence action."). Motiva argues that Plaintiffs have failed to establish damages and causation and requests summary judgment of Plaintiffs' gross negligence claim on the same basis. [20]

***9** The absence of an injury will preclude a negligence claim, even where a clear breach of duty is present. *Rocci v. MacDonald–Cartier*, 323 N.J.Super. 18, 24–25, 731 A.2d 1205 (App.Div.1999) (affirming summary judgment for insufficient evidence of damages in defamation case and noting that "a plaintiff must present proof of a material question of fact as to both liability and damages") (citing *Norwood Easthill Assoc. v. Norwood Easthill Watch*, 222 N.J.Super. 378, 384, 536 A.2d 1317 (App.Div.1988) (affirming summary judgment of malicious interference claim on basis that "plaintiff has suffered no injury or damage")). At the summary judgment stage, Plaintiffs must provide actual evidence of injury and cannot simply rely upon "unsubstantiated allegations." *Trap Rock Indus., Inc. v. Local 825*, 982 F.2d 884, 890 (3d Cir.1992) (reversing district court's denial of summary judgment). Just as "a residential customer not in residence during a power loss, or a commercial customer whose store was closed, might have no damages except the inconvenience of resetting clocks," *Muise*, 371 N.J.Super. at 49, 851 A.2d 799, the release of contaminants into the groundwater aquifer does not itself generate damages, unless Plaintiffs can show that they suffered harm.

Plaintiffs concede that they "have not presented and will not present claims for the present manifested bodily injury." (Undisputed Facts ¶ 67.) However, they argue that they have adequately established damages for medical monitoring and property damage. They do not address their claim for emotional distress. [21]

1. Medical Monitoring

Damages for medical monitoring are appropriate where a plaintiff exhibits no physical injury, but nevertheless requires medical testing as a proximate result of a defendant's negligent conduct. *Ayers v. Jackson Twp.*, 106 N.J. 557, 600, 525 A.2d 287 (1987). The risk of injury need not be quantified to merit medical surveillance damages; however, the plaintiff must establish that the risk of serious disease is "significant." *Id.* at 599–600, 525 A.2d 287; *Campo v. Tama*, 133 N.J. 123, 131, 627 A.2d 135 (1993) (awarding medical monitoring damages to a plaintiff with a "fifty- to seventy-five-percent chance of suffering a recurrence of cancer" due to the delay resulting from defendant doctor's malpractice). In the case of toxic exposure, "medical-surveillance damages may be awarded only if a plaintiff reasonably shows that medical surveillance is required because the exposure caused a distinctive increased risk of future injury." *Theer v. Philip Carey Co.*, 133 N.J. 610, 627, 628 A.2d 724 (1993). Such damages are "not available for plaintiffs who have not experienced direct and hence discrete exposure to a toxic substance and who have not suffered an injury or condition resulting from that exposure." *Id.* at 628, 628 A.2d 724.

Low level contamination, "that is, contamination below the minimum level set by DEP for water remediation," typically is insufficient to establish injurious toxic exposure. *Muralo Co., Inc. v. Employers Ins. of Wausau*, 334 N.J.Super. 282, 290–291, 759 A.2d 348 (App.Div.2000) ("[S]ince it is clear that no untreated groundwater is ever entirely pure, we are satisfied that DEP standards are the most reliable guide for determining whether contamination causing damage ... has occurred."). Here, contaminants have been detected in only eight of Plaintiffs' wells, and no detection has been even close to the GWQS. The NJDEP never restricted Plaintiffs' use of water from their potable wells, nor required Defendant to treat Plaintiffs' wells or to provide Plaintiffs with an alternate water source.

***10** Plaintiffs rely on the testimony of Dr. Michael Gochfeld, Ph.D. ("Gochfeld"), to establish the significant health risks

and necessity of medical surveillance following from the alleged contamination of Plaintiffs' property. However, nothing in Gochfeld's report concludes that the individual Plaintiffs themselves require medical monitoring under the circumstances. Rather, Gochfeld's report creates a medical monitoring program for a hypothetical target population without taking into consideration the actual exposure of any plaintiff.[22] (Gochfeld Dep. at 26–29.) Gochfeld prepared his report under the assumption that "there were known or actual or potential exposure to a variety of constituents of gasoline." (Gochfeld Dep. at 12.) He states in deposition that he had "no specific factual knowledge of the actual exposures in this case," and he confirms that he has never examined the individual Plaintiffs. (Gochfeld Dep. at 10, 29.)

Gochfeld himself notes that "[w]hether a person exposed to MTBE requires medical monitoring depends in large measure on the level of exposure and the time over which it occurred" and notes that "clearly people that are exposed to MTBE casually would not require one." (Gochfeld Dep. at 24.) Furthermore, Gochfeld stated that he "probably would not" recommend medical monitoring for the minor and often single detections of MTBE on Plaintiffs' properties.[23] (Gochfeld Dep. at 46–50.) Consequently, Gochfeld's report does not establish that Plaintiffs require medical monitoring.

Plaintiffs also appear to argue that their wells may have been more contaminated prior to the initiation of Defendant's testing in July 2000. (Opp. at 20.) However, Plaintiffs provide no evidence suggesting that such exposure actually occurred or that any exposure prior to July 2000 was more than minimal. Plaintiffs also argue for the first time in their Opposition that they may have ingested water from contaminated sources besides the potable wells on their property. (Opp. at 20.) However, Plaintiffs offer no evidence that any Plaintiff actually consumed water from CW–8. Without any evidence supporting their theories, Plaintiffs cannot establish a claim for medical monitoring sufficient to survive summary judgment.

Because Plaintiffs have provided no evidence of a "distinctive increased risk of future injury" from the exposure, Plaintiffs are not entitled to damages for medical monitoring.

2. Property Damage

Defendant requests summary judgment of Plaintiffs' claims of property damage on the grounds that the contamination caused no actual damage to Plaintiffs' properties.[24] Instead of claiming that their property was physically harmed, Plaintiffs contend that the news of the contamination stigmatized their property, reducing its value in the minds of potential buyers.

In support of their claim for stigma damages, Plaintiffs offer the expert testimony of Daniel McDonald. However, as discussed previously, McDonald's testimony must be excluded as unreliable. Plaintiffs also argue that the testimony of individual Plaintiffs establishes a stigma discount to their property:

> ***11** Plaintiff Marie Wallace has submitted sworn Interrogatory statements documenting a $150,000.00 loss on the sale of her property. See Exhibit 0 to McKenna Certification. Other Plaintiffs have similarly provided certified answers to Interrogatories and Deposition testimony as to the loss in value through sales transactions, which occurred from the discharge. See Exhibit N–R to the McKenna Certification.

(Opp. at 20–21.)

This evidence fails to establish an injury. Exhibits N–R consist of contracts for sale and unexecuted contracts for sale of three of Plaintiffs' properties, including the Wallace property, leaving it to the Court's imagination to ascertain how these contracts demonstrate a loss in value. Wallace's testimony also fails to establish a stigma injury to the property.

Specifically, Wallace claims that she received a verbal offer for her asking price of $500,000.00 from a man named "Amin," whose last name she cannot recall. (Marie Wallace Dep., McKenna Cert., Ex. 0, M.) Wallace claims that he reneged from the agreement after she told him about the release, however, the alleged offeror never gave Wallace the offer in writing and she has no evidence of the offer or "Amin's" motive for withdrawing, aside from her own testimony. Consequently, even construing this evidence in the light most favorable to Plaintiffs, no reasonable jury could find that Plaintiffs' properties were stigmatized on the basis of this evidence alone.

3. Emotional Distress
Defendant also moves for summary judgment of Plaintiffs' claim for emotional distress. Plaintiffs do not respond to this argument in their Opposition, and Defendant is entitled to summary judgment of Plaintiffs' emotional distress claim for Plaintiffs' failure to present evidence of significant distress or physical injury.

A claim for emotional distress cannot succeed absent evidence of physical injury or "severe and substantial" emotional distress, even where a person has a reasonable concern of an enhanced risk of future disease. *Ironbound Health Rights Advisory Com'n v. Diamond Shamrock Chem. Co.*, 243 N.J.Super. 170, 174–75, 578 A.2d 1248 (App.Div.1990) (noting that "[i]n the absence of physical injury, damages are allowed where the resultant emotional distress is severe and substantial" and listing cases). Without some physical injury, mere exposure to toxic chemicals does not give rise to a claim for emotional distress damages. *Id.* (holding plaintiffs unable to sustain emotional distress claim for exposure to chemicals manufactured at plant near their residences); *see also* *Mauro v. Raymark Indus., Inc.*, 116 N.J. 126, 137, 561 A.2d 257 (1989); *Troum v. Newark Beth Israel Med. Ctr.*, 338 N.J.Super. 1, 17, 768 A.2d 177 (App.Div.2001). Because Plaintiffs provided no evidence of significant emotional distress or physical injury, Defendant's motion for summary judgment will be granted.

B. Trespass
Defendant moves for summary judgment of Plaintiffs' claim for trespass. Plaintiffs argue that Defendant's "intentional refusal" to remove the contamination from their property and failure to install remediation equipment amounts to an intentional trespass. [25] (Opp. at 25.)

***12** The Restatement (Second) of Torts defines intentional trespass as:

> One who intentionally and without a consensual or other privilege
>
> (a) enters land in possession of another or any part thereof or causes a thing or third person so to do, or
>
> (b) remains thereon, or
>
> (c) permits to remain thereon a thing which the actor or his predecessor in legal interest brought thereon in the manner stated in §§ 160 and 161, is liable as a trespasser to the other irrespective of whether harm is thereby caused to any of his legally protected interests.

Rest. (2d) Torts § 158.

As Defendant argues, New Jersey has moved away from "such common law claims as trespass and nuisance" in environmental pollution cases. *Mayor and Council of Borough of Rockaway v. Klockner & Klockner*, 811 F.Supp. 1039, 1053 (D.N.J.1993); *Kenney v. Scientific, Inc.*, 204 N.J.Super. 228, 256, 497 A.2d 1310 (1985) ("There is no need for us ... to torture old remedies to fit factual patterns not contemplated when those remedies were fashioned."). Regardless of the continuing viability of trespass claims in the environmental context, however, Plaintiffs have failed to come forward with any evidence supporting their claim and cannot survive summary judgment.

Plaintiffs note that they are "not arguing that Defendants intentionally caused the contamination of their property," but rather are claiming that "defendants have repeatedly refused to perform the horizontal and vertical delineation of the soil and groundwater contamination in the area of the residential properties." (Opp. at 25.) However, no evidence suggests that such measures were necessary to remove contaminants from Plaintiffs' properties. Rather, the record indicates that Defendant consistently complied with NJDEP requirements, including the installation and maintenance of a groundwater recovery system to rehabilitate the aquifer, and the NJDEP never required Defendant to install any sort of remediation equipment on any of the residences. Given that there has been no detection of a gasoline-related contaminant in any Plaintiff's potable well since April 2001, the argument that Defendant permitted contamination to remain on Plaintiffs' properties lacks any viable evidentiary foundation. Defendant's motion for summary judgment of Plaintiffs' trespass claim will be granted.

C. Strict Liability
Plaintiffs originally claimed a cause of action for strict liability under the theory that the handling, storage, or use of gasoline constitutes an abnormally dangerous activity. However, Plaintiffs voluntarily dismissed this claim in their Opposition. (Pl.'s Opp. at 3.) Accordingly, the Court will not address the merits of Plaintiffs' strict liability claim.

D. Environmental Statutes

1. New Jersey Environmental Rights Act

Plaintiffs allege a right to recover under the New Jersey Environmental Rights Act ("ERA"), N.J.S.A. 2A:35A–1 *et seq.* Defendant requests summary judgment on the grounds that Plaintiffs have not satisfied the ERA's notice provision, N.J.S.A. 2A:35A–11, and that an ERA claim is not actionable where the NJDEP has acted to institute and oversee remediation of the contamination.

***13** Section 4(a) of the ERA, permits "any person" to "maintain an action in a court of competent jurisdiction against any other person to enforce, or to restrain the violation of, any statute, regulation or ordinance which is designed to prevent or minimize pollution, impairment or destruction of the environment." N.J.S.A. 2A:35A–4(a). Although the ERA itself does not create substantive rights, it confers standing on private persons to enforce other environmental statutes, including the New Jersey Spill Compensation and Control Act ("Spill Act"). *Rockaway,* 811 F.Supp. at 1054; *Allied Corp. v. Frola,* 701 F.Supp. 1084, 1091 (D.N.J.1988).

The NJDEP is "entrusted initially with the right to determine the primary course of action to be taken." *Howell Township v. Waste Disposal, Inc.,* 207 N.J.Super. 80, 95, 504 A.2d 19 (App.Div.1986) ("In order to be effective, [the NJDEP] must normally be free to determine what solution will best resolve a problem on a state or regional basis given its expertise and ability to view those problems and solutions broadly."). Consequently, the right of private parties to sue under the EPA is "an alternative to inaction by the government which retains primary prosecutorial responsibility." *Superior Air Prod. Co. v. NL Indus., Inc.,* 216 N.J.Super. 46, 58, 522 A.2d 1025 (App.Div.1987); *Rockaway,* 811 F.Supp. at 1054 ("[T]he primary goal of the ERA is to limit lawsuits by private litigants to those instances where the government has not acted.").

A private ERA suit may be permitted even in the absence of complete government inaction if the NJDEP has "failed in its mission ... failed or neglected to act in the best interest of the citizenry or has arbitrarily, capriciously or unreasonably acted." *Howell,* 207 N.J.Super. at 96, 504 A.2d 19; *Morris County Transfer Station, Inc. v. Frank's Sanitation Serv., Inc.,* 260 N.J.Super. 570, 578, 617 A.2d 291 (App.Div.1992) (permitting private ERA action where the NJDEP would not address violation for three years and had taken no enforcement actions against contaminating defendant who continued operating its illegal facility two months after receiving a violation notice). Where NJDEP "action subsequently proves sufficient to protect the environment," however, NJDEP "action under the Spill Act is preemptive of private rights under ERA." *Superior Air Prod.,* 216 N.J.Super. at 61, 522 A.2d 1025. The permissibility of private action must be evaluated on a case-by-case basis. *Id.*

Here the record indicates consistent and pervasive NJDEP oversight of the remediation process, requiring Defendant to regularly test Plaintiffs' wells and institute interim and permanent groundwater recovery systems. Plaintiffs have not claimed that the NJDEP failed to act or acted unreasonably, and there are no grounds for finding NJDEP inaction sufficient to permit a private ERA suit. Furthermore, as discussed below, Plaintiffs failed to give the NJDEP the requisite notice of their private suit. Accordingly, Defendant's motion for summary judgment of Plaintiffs' ERA claim will be granted.

2. Notice

***14** Before a private party may commence an action under the ERA, the party must "at least 30 days prior to the commencement thereof, direct a written notice of such intention by certified mail, to the Attorney General, the Department of Environmental Protection, the governing body of the municipality in which the alleged conduct has, or is likely to occur, and to the intended defendant." N.J.S.A. 2A:35A–11. The notice provision is intended to give the government an adequate opportunity to intervene in the litigation and to allow the NJDEP:

> to exercise value judgments in individual cases, e.g., whether it will join in that litigation or enforcement proceeding, whether other actions it may have taken already with respect to the particular problem or offender would render the litigation subject to collateral estoppel or res judicata principles, whether its expertise would assist the court, whether broad State interests would be sacrificed unduly to

> regional or personal interests by the instigators of that litigation, etc.

Howell, 504 A.2d at 95; *Morris County,* 260 N.J.Super. at 578, 617 A.2d 291 (quoting *Howell* for same).

Because Plaintiffs did not provide the required thirty day notice to the NJDEP or the Attorney General, they are barred from further pursuing their claim under the ERA. Plaintiffs argue that Defendant is judicially estopped from claiming lack of notice for failure to raise this issue at an earlier stage in the case. Plaintiffs analogize the ERA requirement to that of an affidavit of merit, required in certain cases to avoid "unmeritorious and frivolous malpractice lawsuits at an early stage of litigation." *Knorr v. Smeal,* 178 N.J. 169, 197–98, 836 A.2d 794 (2003) (holding judicially estopped defendant's request for summary judgment for plaintiff's failure to file affidavit of merit) (citing *Palanque v. Lambert–Woolley,* 168 N.J. 398, 404, 774 A.2d 501, 505 (2001)); *Ferreira v. Rancocas Orthopedic Assoc.,* 178 N.J. 144, 836 A.2d 779, (2003) (same).

Defendant argues that the ERA notice requirement is more analogous to the notice of intent in the Resource Conservation and Recovery Act (RCRA), which the Supreme Court held to be a jurisdictional prerequisite to suit in *Hallstrom v. Tillamook County,* 493 U.S. 20, 31, 110 S.Ct. 304, 107 L.Ed.2d 237 (1989) ("[C]ompliance with the 60–day notice provision is a mandatory, not optional, condition precedent for suit."); *Public Interest Research Group of N.J., Inc. v. Windall,* 51 F.3d 1179, 1189 (3d Cir.1995) (holding notice provision jurisdictional in context of Clean Water Act ("CWA")); *Hawksbill Sea Turtle v. Federal Emergency Mgmt. Agency,* 126 F.3d 461, 471 (3d Cir.1997) (holding notice provision jurisdictional in context of Endangered Species Act ("ESA")).

However, the language of the notice requirement in RCRA is not entirely analogous to that of the ERA. RCRA states, under the heading of "Actions prohibited" that "No action may be commenced ... prior to 60 days after the plaintiff has given notice of the violation to" the Administrator, the state and the alleged violator. 42 U.S.C.A. § 6972. The ERA lacks the "no action may be commenced" language of the RCRA, CWA, and ESA, and states only that notice must be sent "at least 30 days prior to the commencement" of suit. Consequently, the argument that the plain language of the statute creates a jurisdictional bar is not as strong in the context of the ERA.

***15** Nevertheless, because the purpose of the notice provision is to provide the Attorney General and NJDEP with notice of the suit and opportunity to intervene, *Howell,* 504 A.2d at 95, and not merely to protect defendants, as in the case of the affidavit of merit, Defendant is not judicially estopped from raising Plaintiffs' lack of compliance with the notice provision and is entitled to summary judgment of Plaintiffs' ERA claim.

E. Spill Act Claim

In their complaint, Plaintiffs assert a private right of action under the Spill Act, N.J.S.A. 58:10–23.11 *et seq.* [26] As amended in 1991, the Spill Act authorizes a private cause of action for individuals to recover costs for environmental damage to their property. *Housing Auth. of City of New Brunswick v. Suydam Inv., L.L.C.,* 177 N.J. 2, 18, 826 A.2d 673 (2003). Actions under the Spill Act are limited to clean up and removal costs, *Bahrle v. Exxon Corp.,* 145 N.J. 144, 155, 678 A.2d 225 (1996), defined as:

> all direct costs associated with a discharge, and those indirect costs that may be imposed by the department pursuant to section 1 of P.L.2002, c. 37 associated with a discharge, incurred by the State or its political subdivisions or their agents or any person with written approval from the department in the: (1) removal or attempted removal of hazardous substances, or (2) taking of reasonable measures to prevent or mitigate damage to the public health, safety, or welfare, including, but not limited to, public and private property.
>
> N.J.S.A. 58:10–23.11b(d). The Act does not authorize "damages arising from emotional distress, enhanced risk of disease, loss of enjoyment of property, and other economic and financial harm." *Bahrle,* 145 N.J. at 155, 678 A.2d 225.

Plaintiffs maintain that the investigation conducted by Ellwood was a reimbursable clean up and removal cost under the Spill Act. As Plaintiffs suggest, because "a discharge cannot be addressed until the contaminants are defined and the extent of the discharge determined," certain forms of investigative costs are implicitly included in the Act. *Metex Corp. v. Federal Ins. Co.,* 290 N.J.Super. 95, 115, 675 A.2d 220 (App.Div.1996).

However, for a private party to obtain reimbursement under the Act, the party must have obtained "written approval from the department," for example, in a memorandum of agreement, prior to incurring the cost. N.J.S.A. 58:10–23.11b(d); *Id.* Such approval permits the NJDEP to "review and approve or disapprove its investigation to date, its proposed remedial action, and its report of the implementation of its action." *Id.; see also Interfaith Cmty Org. v. Honeywell Intern., Inc.*, 263 F.Supp.2d 796, 867 (D.N.J.2003) (concluding "that such costs were approved by and/or incurred at the direction of NJDEP and thus are recoverable under the Spill Act."). Because Plaintiffs have not obtained NJDEP approval for any cost incurred, including the Ellwood report, Defendant is entitled to summary judgment of Plaintiffs' Spill Act Claim.

*16 The accompanying Order shall enter today.

Elcock, 233 F.3d at 741.

All Citations

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Footnotes

1 The following facts are taken from Defendant's statement of undisputed material facts, filed June 24, 2005, ("Undisputed Facts") and Plaintiffs' counterstatement of undisputed facts, filed Oct. 14, 2005, ("Counterstatement Facts"). Plaintiffs did not provide a separate statement of undisputed facts.
Although Plaintiffs dispute the majority of Defendant's statements of fact, Plaintiffs' counterstatements typically provide additional facts without setting forth any conflicting evidence. Where no actual disputes are presented, Defendant's statements will be treated as undisputed. *See e.g., Tofano v. Reidel,* 61 F.Supp.2d 289, 292 n. 1 (D.N.J.1999) (citing Fed.R.Civ.P. 56(e)) ("This court will ... not consider assertions without evidential support as creating genuine issues of disputed fact."); *Talbot v. United States,* 2005 WL 2917463, *2 (D.N.J.2005) (noting that where the nonmoving party does not submit facts in opposition, "it is entirely appropriate for this court to treat all facts properly supported by the movant to be uncontroverted") (quoting *Allebach v. Sherrer,* No. 04–287, 2005 U.S. Dist. LEXIS 15626, at *5 (D.N.J.2005)).
More generally, Plaintiffs' brief suffers from numerous typographical errors and a dearth of citations to page numbers in the record. This "alone warrants exclusion of the evidence." *See Orr v. Bank of America, NT & SA,* 285 F.3d 764, 774–75 (9th Cir.2002) (holding that party's failure to cite page and line numbers when referencing the deposition merits exclusion of evidence); *Huey v. UPS, Inc.,* 165 F.3d 1084, 1085 (7th Cir.1999) ("[J]udges need not paw over the files without assistance from the parties."); *Nissho–Iwai Am. Corp. v. Kline,* 845 F.2d 1300, 1307 (5th Cir.1988) (parties must designate specific facts and their location in the record).

2 Among the original litigants to the suit were also former plaintiffs Michael and Susan Kammerhoff and Norma Simmons. The Kammerhoff plaintiffs were voluntarily dismissed, and plaintiff Norma Simmons died on August 26, 2000.

3 VOCs generally associated with gasoline discharge include MTBE, benzene, toluene, ethylbenzene, xylene (collectively "BTEX"), and tertiary butyl alcohol ("TBA"). The NJDEP has issued a Ground Water Quality Standard ("GWQS") for each of these VOCs, also known as "gasoline-related compounds." MTBE, for example, has a GWQS of 70 parts per billion ("ppb").

4 Although Motiva detected MTBE in thirteen residential wells, not all of these wells are owned by Plaintiffs to this litigation. Of the twenty-seven parcels of property at issue in this suit, only eight of the properties contain wells that ever tested positive for any gasoline-related compound.

5 The direction of water's flow in an aquifer is described as "downgradient," and the direction against the current is "upgradient."

6 In particular, testing revealed emissions in monitoring wells 6–Shallow ("MW–6S") and 7–Deep ("MW–7D"), which lie between the Motiva site and the residential properties. However, the majority of upgradient monitoring wells did not test positive for gasoline-related contaminants. (NJDEP Directive, March 21, 2001 ("March 2001 Directive"), Mairo Cert. in Supp. Def.'s Mot. Summ. J., filed June 24, 2005 ("Mairo Cert."), Ex. O, at 4.)

7 Plaintiffs dispute Defendant's characterization of the CEA, (Counterstatement Facts ¶ 31), on the basis that Defendant proposed the CEA prior to conducting an actual delineation of the plume and that "the Plaintiffs' residential wells could only had [sic] been included in the CEA, if Defendant intended to supply a permanent public water supply to Plaintiffs' properties." While Plaintiffs' contention with the CEA is not entirely clear, Plaintiffs have not provided any evidence indicating that the NJDEP improperly approved the CEA or that the CEA was an inaccurate representation of the boundaries of contaminants in excess of the GWQS.

8 Plaintiffs' properties are: 850 Sicklerville Road; 565, 569, 581, and 583 Berlin–Cross Keys Road; 6, 9, 10, 12, 13, 14, 1, 16, 17, 18, 20 Spring Hollow; 2, 4, 6, and 8 Latham Way; 3, 4, 5, 7, 12, 14, and 15 Donna Marie Court.

9 CW–8 is located approximately 1,000 feet downgradient of the contamination site. (March 2001 Directive at 2.) While active, CW–8 pumps approximately 500 gallons per minute and causes the groundwater to flow southwest. (Ellwood Report at 2.) When CW–8 is not pumping, the groundwater flow is more westerly. (Ellwood Report at 2.)

10 Plaintiff disputes these facts on the basis that:

> The Defendant has no data for any portable [sic] water supply of the Plaintiffs prior to July 2000. The Defendant never performed any delineation of the groundwater plume in the areas of the residential properties despite having actual knowledge of such contamination in MW–6, MW–7 and MW–12. See Gallo Certification and Exhibits C, D and E.

(Counterstatement Facts ¶¶ 46–48.) However, because Defendant makes no averment of the presence or absence of contamination prior to July 2000, Defendant's statements are not actually in dispute. Plaintiffs provide no fact indicating an inaccuracy in Defendant's statements regarding the testing of Plaintiffs' wells. Consequently, there is no actual dispute regarding the presence or amount of *detected* gasoline-related compounds.

11 Plaintiffs dispute these statements by citing to Exhibit F of the McKenna certification; however, Exhibit F is the Ellwood report and therefore is not indicative of the NJDEP requirements. Plaintiffs nowhere cite to a statement by the NJDEP requiring Defendant to treat their water or provide them with an alternate water source, and therefore this fact is undisputed.

12 Because this Court will grant Defendant's motion for summary judgment, it will not reach the merits of Defendant's motions to exclude experts Gochfeld, Ellwood, and Gallo.

13 After *Daubert,* Rule 702 was amended to encompass the *Daubert* analysis:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed.R.Evid. 702. While *Daubert* itself addressed only the admissibility of scientific evidence, the Court has since noted that courts' gatekeeping obligations extend to all expert testimony. *Kumho Tire Co. v. Carmichael,* 526 U.S. 137, 151, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999).

14 The Court noted that it had "misgivings" about the expert's qualifications in spite of:

> (1) [the expert's] general training in "assessing" individuals, which he received while earning his Ph.D. in psychology; (2) his experience, twenty years previous, helping drug addicts reenter the workforce; (3) his experience primarily in the last two years dealing with the Virgin Islands Division of Workers' Compensation, which he had advised regarding the ability of approximately fifty to sixty-five disabled employees to return to their previous jobs; (4) his past experience as an expert witness making lost earning capacity assessments;

(5) his attendance at two seminars regarding vocational rehabilitation, and his stated familiarity with the literature in the area; (6) his membership in two vocational rehabilitation organizations, both of which place no restrictions on membership; and (7) the fact that when [the expert] was in school, a degree in vocational rehabilitation therapy was not available, but that he received similar training nonetheless.

15 Plaintiffs also argue that "Defendant does not attack the methodology, standard or factual basis for the opinions," (Opp. at 31), however, it is quite clear from Defendant's motion that the reliability of McDonald's methodology is hotly disputed.

16 McDonald also appeared unaware of the fact that Plaintiffs' properties are served by potable wells, even though the potable wells contain the evidence of contamination.

Q: Do you know whether or not the plaintiffs' properties have potable wells?

A: It's my understanding that they are hooked to a public water system.

Q: If each of the properties did in fact have a potable well, would that be a factor that you were consider relevant in your analysis?

Mr. McKenna: You may want to review the documents that you referenced in your report to assist you in this area. Just separate the Ellwood and Gallo reports. I'm going to go to the men's room.

(Whereupon, a recess is taken.)

Mr. Mairo: I am going to object that Mr. McKenna was basically coaching the witness.

Back on the record.

A: Your question about whether or not each of these houses were, was, had their own private well on site-

Q: Uh-huh?

A: -it's my understanding that each house is served by wells within and around the neighborhood and that Consumer, Consumers Water Company owns those wells and supplies that water to the homes.

(McDonald Dep. at 36.)

17 McDonald reaches the 35% devaluation figure with the following methodology:

The subject properties are in the early stages of monitoring, and clean up of the ground water contamination. The properties from Dover Twp. are beyond the clean up stage and into the final stage of recovery, yet they still show a 13% loss in value as compared to similar properties outside of the contaminated area. The subject area is in stage D of recovery, which is the beginning of the remediation process. Based on the acceptance of the Detrimental Condition Model as a viable process for valuing Detrimental Conditions to Real Estate, by the appraisal community and the Subcommittee on Housing and Community Opportunity of the House Committee on Financial Services, it would be logical to assume that the discount to the properties which are the subject of this report, would be 2 to 3 times that of properties in the final stage of recovery. In this case a discount of 35% would be considered reasonable.

(McDonald Report at 31.)

18 Interbay Funding, for example, qualified their statement that they would not lend by noting, "The property would have to be completely cleaned up. They would have to file all necessary documents to the state of NJ and we would require something from the state telling us the property is cleaned up." (McDonald Report at 32.) From this, McDonald concluded that Interbay Funding would not lend on properties such as Plaintiffs', without considering that none of Plaintiffs' properties were contaminated in excess of state standards.

19 In evaluating this data, McDonald states:

The lenders that did respond have overwhelmingly stated that they would not approve the loan at all, or they would require substantial conditions to the loan. In the case of the subject properties, it can be assumed that a purchaser with private financing or cash would be the only potential buyer of houses in this area.

(McDonald Report at 32.)

20 Because the Court now finds that there is no evidence of any actual injury arising from Defendant's negligence, this Court will not address Defendant's causation argument.

21 Plaintiff argues that Defendant's motion for summary judgment of its negligence claim should be denied on the basis of the doctrine of *res ipsa loquitur*. However, *res ipsa loquitur* acts only to "permit[ ] an inference of defendant's negligence" (i.e., that defendant acted in an unreasonable manner) under particular

circumstances. *Jerista v. Murray,* 185 N.J. 175, 192, 883 A.2d 350 (2005). The doctrine does not establish either causation or the presence of damages. *See e.g., Bahrle v. Exxon Corp.,* 279 N.J.Super. 5, 35, 652 A.2d 178 (App.Div.1995) (holding *res ipsa* doctrine inapplicable where "there was a factual dispute as to whether the contamination was a result of plaintiffs' own voluntary acts or neglect"). Accordingly, because Defendant is contesting only causation and damages, the *res ipsa* doctrine does not apply.

22 Gochfeld testifies in his deposition that he created his report without any specific information about the Plaintiffs:

> Q: So, for example, in determining the percentage of the target population that was in high exposure category, that wasn't based on the ground water, your review of the ground water tables that were attached to Mr. Gallo's report?
>
> A: It was not.
>
> Q: That was based purely on just an assumption of yours?
>
> A: It was an assumption based on experience with previous programs or programs that are currently underway in our communities.
>
> Q: Having no specific factual knowledge of the actual exposures in this case?
>
> A: That's correct, these are hypotheticals.

(Gochfeld Dep. at 28–29.)

23 Gochfeld also states that he would not even recommend medical monitoring for the one property with by far the highest detection of MTBE (13.8 ppb at 4 Latham Way) "on this data alone" because "[i]t is possible that a person living there would only be drinking bottled water, would not be in the house very much." (Gochfeld Dep. at 50.)

24 Defendant argues further that New Jersey law does not permit Plaintiffs to recover for stigma damages in the absence of some physical harm to their property. Because Plaintiffs have provided no evidence of any stigma to their property, the Court will not reach Defendant's alternative argument.

25 It is unclear whether Plaintiffs allege negligent trespass since they discuss only the Restatement (Second) of Torts § 158, Intentional Trespass, in their Opposition. Unlike intentional trespass, negligent or reckless trespass requires evidence of "harm to the land, to the possessor, or to a thing or a third person." Rest. Torts 2d § 165; *see also Burke v. Briggs,* 239 N.J.Super. 269, 271, 571 A.2d 296 (App.Div.1990) (citing Rest.2d Torts § 158 with approval for another premise); *Karpiak v. Russo,* 450 Pa.Super. 471, 481, 676 A.2d 270 (Pa.Super.1996) (affirming dismissal of trespass claim for entry of dust onto property since the "evidence failed to establish that the dust caused appellants harm"). As discussed previously, Plaintiffs have not provided any evidence of injury to their persons or property. Consequently, to the extent that Plaintiffs are claiming negligent trespass, Defendant is entitled to summary judgment.

26 It is unclear whether Plaintiffs also raise a claim for cleanup and removal costs from the Spill Compensation Fund under N.J.S.A. 58:10–23.11g(a). (Opp. at 12–13.) However, the appropriate procedure to obtain compensation under the Fund is by filing a claim with the administrator of the Fund, "not later than one year after the date of discovery of damage. The administrator shall prescribe appropriate forms and procedures for such claims." N.J.S.A. 58:10–23.11k. In the event "a party, including a potentially responsible party ... contests the amount or validity of" a claim for reimbursement from the Spill Fund, "the dispute is referred to an arbitrator whose decision may be appealed to the Appellate Division," and the arbitrator's decision will be final unless it was "arbitrary, capricious, or unreasonable." *Lacey Municipal Util. Auth. v. New Jersey Dept. of Envir. Prot., Envir. Claims Admin.,* 369 N.J.Super. 261, 273, 848 A.2d 843 (App.Div.2004). Accordingly, this is an improper forum for a Spill Compensation Fund claim.

End of Document

Exhibit P

FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan)

Get updates on the recalls

Update: 11/13/2019 - FDA warns Mylan for CGMP deviations

Update [11/13/2019] Today, the U.S. Food and Drug Administration posted a warning letter (/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/mylan-laboratories-limited-unit-8-589297-11052019) to Mylan Pharmaceuticals, Inc. in Chodavaram Village, Vizianagaram, Andhra Pradesh, India. Mylan manufactures valsartan active pharmaceutical ingredient (API) and has been one subject of an ongoing global investigation into nitrosamine impurities in angiotensin II receptor blockers (ARBs) such as valsartan, losartan and irbesartan.

The warning letter outlines several current good manufacturing practice (CGMP) deviations at this Mylan facility, including failure to have adequate written procedures for the receipt, identification and handling of raw materials and failure to adequately clean equipment and utensils. Failure to correct these deviations may result in further action by the agency. The warning letter is another result of the agency's ongoing investigation.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

Update: 10/15/2019 - FDA warns Torrent for CGMP violations

Update [10/15/2019] Today, the U.S. Food and Drug Administration posted a warning letter (/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/torrent-pharmaceuticals-limited-585255-10082019) to Torrent Pharmaceuticals in Ahmedabad, Gujarat, India. Torrent manufactures losartan potassium tablets and has been one subject of an ongoing global investigation into nitrosamine impurities in angiotensin II receptor blockers (ARBs) such as valsartan, losartan and irbesartan.

The warning letter outlines several manufacturing violations at Torrent's Taluka-Kadi, Indrad, Gujarat facility, including failure to follow written procedures for production and process control and failure to adequately investigate batch discrepancies. Failure to correct

these violations may result in further action by the agency. The warning letter is another result of the agency's ongoing investigation.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

Update: 9/20/2019 - Torrent expands its voluntary recall of losartan

Update [9/20/2019] Torrent Pharmaceuticals is expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium-0) to include five additional lots of losartan potassium tablets (three lots of losartan potassium tablets and two lots of losartan potassium/hydrochlorothiazide (HCTZ) combination tablets). This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited. Torrent is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.
The agency updated the list of recalled angiotensin II receptor blockers (ARBs) (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and) accordingly.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

8/28/2019: STATEMENT: Statement on the agency's ongoing efforts to resolve safety issue with ARB medications

Go to FDA Statement (/news-events/press-announcements/statement-agencys-ongoing-efforts-resolve-safety-issue-arb-medications)

6/26/2019: UPDATE - Macleods Pharmaceuticals voluntarily recalls losartan containing NMBA

Update [6/26/2019] FDA is alerting patients and health care professionals to Macleods Pharmaceuticals' voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/macleods-pharmaceutical-limited-issues-voluntary-nationwide-consumer-level-recall-losartan-potassium) of two lots of losartan potassium tablets (50mg strength) and 30 lots of losartan potassium/hydrochlorothiazide (HCTZ) combination tablets (12 lots of

50mg/12.5mg strength, three lots of 100mg/12.5mg strength, and 15 lots of 100mg/25mg strength). This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs). The agency also updated the list of recalled angiotensin II receptor blockers (ARBs) (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and) .

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

6/12/2019: UPDATE - Teva expands its voluntary recall of losartan

Update [6/12/2019] Teva Pharmaceuticals is expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/teva-pharmaceuticals-usa-inc-expands-voluntary-nationwide-recall-losartan-potassium-50-mg-and-100-mg) to include seven additional lots of losartan potassium tablets (three lots of 50 mg strength and four lots of 100 mg strength) labeled by Golden State Medical Supply. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited. Teva is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

The agency updated the list of recalled angiotensin II receptor blockers (ARBs) (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and) accordingly.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

5/6/2019: UPDATE - FDA alerts patients and health care professionals to Vivimed's recall of losartan medication due to NMBA

Update [5/6/2019] FDA is alerting patients and health care professionals to a voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/vivimed-life-sciences-pvt-ltd-issues-voluntary-nationwide-recall-losartan-potassium-25-mg-50-mg-and) of 19 lots of

losartan potassium tablets made by Vivimed Life Sciences Pvt Ltd in Alathur, Chennai, India and distributed by Heritage Pharmaceuticals Inc, East Brunswick, New Jersey, due to the detection of the impurity N-Nitroso-N-methyl-4-aminobutyric acid (NMBA). Vivimed is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit (https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan#interimlimits2) of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

FDA reminds patients taking recalled angiotensin II receptor blockers (ARBs) to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

The agency also updated the list of recalled ARBs (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and).

5/2/2019: UPDATE - Laboratory analysis of valsartan products

Update [5/2/2019] FDA posted laboratory test results showing NDEA levels in recalled valsartan products (/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products) as well as an assessment of the cancer risk from NDEA in valsartan.

4/29/2019: UPDATE - FDA alerts patients and health care professionals to Teva's recall and Legacy's expanded recall of losartan medication due to NMBA

Update [4/29/2019] FDA is alerting patients and health care professionals to a voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/teva-pharmaceuticals-usa-inc-issues-voluntary-nationwide-recall-losartan-potassium-25-mg-and-100-mg) of 44 lots of losartan potassium tablets manufactured by Teva Pharmaceuticals and labeled as Golden State Medical Supply due to the detection of the impurity N-Nitroso-N-methyl-4-aminobutyric acid (NMBA). The recalled products were made with active pharmaceutical ingredient (API) manufactured by Hetero Labs. Teva is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.
Additionally, Legacy expanded its recall (/safety/recalls-market-withdrawals-safety-alerts/legacy-pharmaceutical-packaging-llc-expands-voluntary-nationwide-recall-losartan-potassium-tablets) to include one additional lot of losartan tablets made with API

manufactured by Hetero Labs.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

The agency also updated the list of recalled losartan medicines (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and).

4/19/2019: UPDATE - Torrent further expands its voluntary recall of losartan; FDA posts new nitrosamine testing methods

Update [4/19/2019] Torrent Pharmaceuticals Limited is further expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium) to include 104 additional lots of losartan potassium and losartan potassium/hydrochlorothiazide combination tablets. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.
The agency updated the list of losartan products under recall (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and) accordingly.

FDA reminds patients taking recalled angiotensin II receptor blockers (ARBs) to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

FDA is also posting new testing methods which can help manufacturers and international regulators detect and identify multiple nitrosamine impurities. FDA and international regulators have identified N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA) and NMBA in ARBs.

- A direct injection GC-MS method (/media/123409/download) that is able to detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), and N-nitrosodibutylamine (NDBA)
- A headspace GC-MS method (/media/124025/download) that is able to detect NDMA, NDEA, NDIPA, and NEIPA

These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

4/4/2019: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on the agency's list of known nitrosamine-free valsartan and ARB class medicines, as part of agency's ongoing efforts to resolve ongoing safety issue

Go to FDA Statement (/news-events/press-announcements/fda-statement-agencys-list-known-nitrosamine-free-valsartan-and-arb-class-medicines-part-agencys)

3/22/2019: UPDATE - FDA updates recalled valsartan-containing and losartan-containing medicine information

Update [3/22/2019] FDA has updated the list of valsartan medicines under recall (/media/118231/download) to incorporate additional repackagers of Aurobindo's valsartan-containing medicine. FDA has also updated the list of losartan medicines under recall (/media/119422/download) to include repackagers of Torrent's and Camber's losartan-containing medicines.

The agency also updated the list of valsartan medicines not under recall (/media/118232/download) accordingly.

3/20/2019: UPDATE - FDA not objecting to losartan with NMBA below 9.82 ppm remaining on the market

Update [3/20/2019] To ensure patient access to losartan, FDA will not object to certain manufacturers temporarily distributing losartan containing N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) above the interim acceptable intake limit of 0.96 parts per million (ppm) and below 9.82 ppm until the impurity can be eliminated. The agency expects many companies will be able to manufacture losartan without nitrosamine impurities and replenish the U.S. supply in approximately six months.

Agency scientists evaluated the risk of exposure to NMBA at levels up to 9.82 ppm and determined that it presents no meaningful difference in cancer risk over a six-month time period when compared to a lifetime of exposure to NMBA at 0.96 ppm. Distributing losartan containing NMBA up to 9.82 ppm, will help maintain adequate losartan supply while companies obtain approval for manufacturing processes that produce nitrosamine-free losartan for patients.

FDA reminds patients taking recalled losartan to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. Untreated hypertension (high blood pressure) leads to an increase in the risk of heart attacks and stroke. Untreated heart failure increases the risk of hospitalization and death. Untreated diabetic nephropathy (kidney disease) leads to worsening renal (kidney) disease.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

FDA continues to work with companies and international regulators to ensure products entering the U.S. market do not contain nitrosamine impurities.

3/1/2019: UPDATE - Torrent again expands its voluntary recall of losartan; Hetero also voluntarily recalls losartan

Update [3/1/2019] Torrent Pharmaceuticals Limited is further expanding its voluntary recall (Updated: Torrent Pharmaceuticals Limited Issues Voluntary Nationwide Recall of Losartan Potassium Tablets, USP and Losartan Potassium /Hydrochlorothiazide Tablets, USP) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) to include 114 additional lots of losartan potassium and losartan potassium/hydrochlorothiazide combination tablets. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Today, the agency also issued a press release (FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall) to provide additional information about its ongoing investigation and another voluntary recall by Hetero/Camber Pharmaceuticals, which was announced on February 28, of 87 lots of losartan potassium tablets (25 mg, 50 mg and 100 mg). The recalled losartan potassium and losartan potassium/hydrochlorothiazide tablets are also manufactured by Hetero, which are distributed by Camber, and contain the impurity NMBA.

Torrent and Hetero/Camber are only recalling lots of losartan-containing medication with NMBA above the interim acceptable intake limits of 0.96 parts per million (ppm).

The agency also updated the list of losartan products under recall (/media/119422/download).

3/1/2019: UPDATE - Aurobindo expands its voluntary recall of valsartan and amlodipine/valsartan

Update [3/1/2019] AurobindoPharma USA is expanding its voluntary recall (AurobindoPharma USA, Inc. Initiates a Voluntary Nationwide Consumer Level Recall Expansion of 38 Lots of Amlodipine Valsartan Tablets USP and Valsartan Tablets, USP due to the detection of NDEA (N-Nitrosodiethylamine) Impurity.) to include 38 additional lots of valsartan and amlodipine/valsartan combination tablets. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) found in the medicine.

Aurobindo is only recalling lots of valsartan-containing medication where NDEA has been detected above the interim acceptable intake limit of 0.083 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs).

The agency also updated the valsartan products under recall (/media/118231/download).

3/1/2019: PRESS RELEASE - FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall

Go to Press Release (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632425.htm)

FDA updates table of interim limits for nitrosamine impurities in ARBs

Update [2/28/2019] FDA is posting the updated table of interim acceptable intake limits for nitrosamine impurities to reflect N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) limits, which are the same as those for NDMA.

The agency will use the interim limits below to recommend manufacturers conduct a voluntary recall if laboratory testing confirms the presence of nitrosamine impurities in finished drug product. FDA is working with industry and international regulators to ensure products entering the market do not contain these impurities, but we are tolerating the impurities below the level established in the table for a short period of time to avoid a possible shortage of ARBs.

Not all ARB products contain NDMA, NDEA or NMBA impurities, so pharmacists may be able to provide an alternative medication not affected by the recalls, or health care professionals may prescribe a different medication that treats the same condition.

Interim Limits for NDMA, NDEA, and NMBA in Angiotensin II Receptor Blockers (ARBs)

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake NDMA (ng/day)*	Acceptable Intake NDMA (ppm)**	Acceptable Intake NDEA (ng/day)*	Acceptable Intake NDEA (ppm)**	Acceptable Intake NMBA (ng/day)*	Acceptable Intake NMBA (ppm)**
Valsartan	320	96	0.3	26.5	0.083	96	0.3
Losartan	100	96	0.96	26.5	0.27	96	0.96***
Irbesartan	300	96	0.32	26.5	0.088	96	0.32
Azilsartan	80	96	1.2	26.5	0.33	96	1.2
Olmesartan	40	96	2.4	26.5	0.66	96	2.4
Eprosartan	800	96	0.12	26.5	0.033	96	0.12
Candesartan	32	96	3.0	26.5	0.83	96	3.0
Telmisartan	80	96	1.2	26.5	0.33	96	1.2

* The acceptable intake is a daily exposure to a compound such as NDMA, NDEA, or NMBA that approximates a 1:100,000 cancer risk after 70 years exposure
** These values are based on a drug's maximum daily dose as reflected in the drug label
*** FDA is temporarily not objecting to losartan with NMBA below 9.82 ppm remaining on the market

2/25/2019: UPDATE - Losartan distributed by Macleods Pharmaceuticals voluntarily recalled

Update [2/25/2019] FDA is alerting patients and health care professionals to a voluntary recall of one lot of losartan potassium/hydrochlorothiazide (HCTZ) 100mg/25mg combination tablets manufactured by Macleods Pharmaceuticals. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) found in the medicine made with active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Macleods is only recalling lots of losartan-containing medication where NDEA has been detected above the interim acceptable intake limit of 0.27 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs).

The agency also updated the list of losartan products under recall (/media/119422/download).

1/25/2019: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues

Go to FDA Statement (/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps)

1/23/2019: UPDATE - Torrent further expands its voluntary recall of losartan

Update [1/23/2019] Torrent Pharmaceuticals is further expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-losartan-potassium) to include six additional lots of losartan potassium and hydrochlorothiazide combination tablets, for a total of 16 lots of losartan-containing medicines. This recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Torrent is only recalling lots of losartan-containing medication containing NDEA above the interim acceptable intake limits of 0.27 parts per million (ppm).

The agency also updated the list of losartan medications under recall (/media/119422/download).

1/18/2019: UPDATE - Irbesartan distributed by Solco Healthcare voluntarily recalled

Update [1/18/2019] FDA is alerting patients and health care professionals to a voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/prinston-pharmaceutical-inc-issues-voluntary-nationwide-recall-irbesartan-and-irbesartan-hctz) of one lot of irbesartan and seven lots of irbesartan and hydrochlorothiazide (HCTZ) combination tablets distributed by Solco Healthcare LLC, a Prinston Pharmaceutical Inc. subsidiary. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) in the irbesartan active pharmaceutical ingredient manufactured by Zhejiang Huahai Pharmaceuticals (ZHP).

Solco is only recalling lots of irbesartan-containing medication where NDEA has been detected above the interim limit of 0.088 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin receptor II blockers (ARBs).

The agency also updated the list of irbesartan products under recall.

1/3/2019: UPDATE - Torrent expands its voluntary recall of losartan

Update [1/3/2019] Torrent Pharmaceuticals is expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium-tablets-usp) to include eight additional lots of losartan potassium tablets, for a total of 10 lots. This recall is due to trace amounts of N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

Torrent is only recalling lots of losartan medication containing NDEA above the interim acceptable intake level of 0.27 parts per million.

The agency also updated the list of list of valsartan products under recall (/media/118231/download).

1/2/2019: UPDATE - FDA alerts patients and health care professionals to Aurobindo's recall of valsartan medication due to NDEA

Update [1/2/2019] FDA is alerting patients and health care professionals to Aurobindo Pharma USA's voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-usa-inc-initiates-voluntary-nationwide-consumer-level-recall-80-lots-amlodipine) of two lots of valsartan tablets, 26 lots of amlodipine and valsartan combination tablets, and 52 lots of valsartan and hydrochlorothiazide (HCTZ) combination tablets due to the amount of N-Nitrosodiethylamine (NDEA) in the valsartan active pharmaceutical ingredient. Aurobindo is recalling amlodipine and HCTZ only in combination medications containing valsartan. Neither amlodipine nor HCTZ is currently under recall by itself.

Aurobindo is recalling lots of valsartan-containing medication that tested positive for NDEA above the interim acceptable daily intake level of 0.083 parts per million.

The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above interim acceptable daily intake levels.

FDA also updated the list of valsartan products under recall (/media/118231/download) and the list of valsartan products not under recall (/media/118232/download).

FDA reminds patients taking any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. Some ARBs contain no NDMA or NDEA.

12/20/2019: UPDATE - FDA alerts patients and health care professionals to Torrent's recall of losartan medication due to NDEA

Update [12/20/2018] FDA is alerting patients and health care professionals to Torrent Pharmaceuticals'
voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-losartan-potassium) of two lots of losartan potassium 100 mg tablets due to N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

Not all Torrent losartan-containing medications distributed in the U.S. are being recalled. Torrent is recalling only those lots of losartan medication that tested positive for NDEA above the acceptable daily intake of 0.27 ppm.

The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above acceptable daily intake levels.

FDA posted a list of losartan medications under recall (/media/119422/download). Additionally, FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

12/19/2018: UPDATE - FDA presents interim limits of nitrosamines in currently marketed ARBs

Update [12/19/2018] FDA is publishing interim acceptable intake levels of nitrosamine impurities in angiotensin II receptor blockers (ARBs) for manufacturers to use to ensure their finished drug products are safe for patients.

The agency evaluated safety data for N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) to determine an interim acceptable intake level for these impurities in the ARB class. NDMA and NDEA are probable human carcinogens and should

not be present in drug products. We are currently aware of NDMA and NDEA in certain valsartan, irbesartan and losartan-containing products, and those products and some active pharmaceutical ingredients (API) used to manufacture them have been recalled from the U.S. market. See the list of valsartan products under recall (/media/118231/download) and the list of irbesartan products under recall (/media/118233/download).

Drug products that contain NDMA or NDEA above the limits in the table below pose an unacceptable risk to patients. The agency will use the interim limits to recommend manufacturers conduct a voluntary recall if laboratory testing confirms the presence of nitrosamine impurities in finished drug product. FDA is working with industry and international regulators to ensure products entering the market do not contain these impurities, but we are tolerating the impurities below the level established in the table for a short period of time to avoid a possible shortage of ARBs.

The agency reminds manufacturers they are responsible for developing and using suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects a new impurity or higher level of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients. To aid industry and regulatory agencies, FDA has developed and published methods to detect NDMA and NDEA impurities – the gas chromatography/mass spectrometry (GC/MS) headspace method (/media/115965/download), the combined GC/MS headspace method (/media/117843/download), and the combined GC/MS direct injection method (/media/117807/download). These methods can be used for drug substances and products, and users should validate them as part of good manufacturing practices and where data are used to support a regulatory submission or required quality assessment of the API or drug product.

Not all ARB products contain NDMA or NDEA impurities, so pharmacists may be able to provide an alternative medication not affected by the recalls, or health care professionals may prescribe a different medication that treats the same condition.

Interim Limits for NDMA and NDEA in Angiotensin II Receptor Blockers (ARBs)

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake NDMA (ng/day)*	Acceptable Intake NDMA (ppm)**	Acceptable Intake NDEA (ng/day)*	Acceptable Intake NDEA (ppm)**
Valsartan	320	96	0.3	26.5	0.083
Losartan	100	96	0.96	26.5	0.27
Irbesartan	300	96	0.32	26.5	0.088

Azilsartan	80	96	1.2	26.5	0.33
Olmesartan	40	96	2.4	26.5	0.66
Eprosartan	800	96	0.12	26.5	0.033
Candesartan	32	96	3.0	26.5	0.83
Telmisartan	80	96	1.2	26.5	0.33

* The acceptable intake is a daily exposure to a compound such as NDMA or NDEA that results in a 1:100,000 cancer
risk after 70 years exposure
** These values are based on a drug's maximum daily dose as reflected in the drug label

For comparison with the levels of NDMA found in some common foods, please see our Aug. 20, 2018, update.

12/12/2018: UPDATE - FDA updates NDMA and NDEA detection methods, announces posting of ZHP warning letter

Update [12/12/2018] The FDA has updated its testing methods to detect NDMA and NDEA impurities – the (([!--$ssDownloadLink('UCM618053')--])GC/MS) headspace method (/media/115965/download), the combined headspace method (/media/117843/download), and the combined direct injection method (/media/117807/download) – by adding the limits of detection (LOD) and clarifying that the methods can be used for both drug substances and drug products. These methods were validated with respect to valsartan drug substances and drug products, but the agency expects them to have comparable LODs and limits of quantitation (LOQ) for other angiotensin II receptor blockers (ARB).

The agency also issued a press release announcing the posting of a warning letter the agency issued Nov. 29 to Zhejiang Huahai Pharmaceuticals Co. Ltd. (ZHP).

12/11/2018: PRESS RELEASE - FDA warns API manufacturer involved in valsartan recall, provides information for patients taking these medications

Go to Press Release (/news-events/press-announcements/fda-warns-api-manufacturer-involved-valsartan-recall-provides-information-patients-taking-these)

12/6/2018: UPDATE - Mylan expands its voluntary recall of valsartan-containing products

Update [12/6/2018] Mylan Pharmaceuticals is expanding its voluntary recall ([!--$wcmUrl('link','UCM627647')--])to include all lots of non-expired valsartan-containing products due to trace amounts of N-Nitrosodiethylamine (NDEA) in the valsartan active pharmaceutical ingredient (API) manufactured by Mylan Laboratories Limited. The 104 additional lots include 26 lots of amlodipine and valsartan tablets, 51 lots of valsartan tablets and 27 lots of valsartan and hydrochlorothiazide tablets. These lots were distributed in the U.S. between March 2017 and November 2018.

The agency also updated the list of valsartan products under recall (/media/118231/download) and the list of valsartan products not under recall (/media/118232/download).

11/27/2018: UPDATE - FDA alerts patients and health care professionals to Teva's recall of valsartan products due to NDEA

Update [11/27/2018] FDA is alerting patients and health care professionals to Teva Pharmaceuticals' voluntary recall (/safety/recalls-market-withdrawals-safety-alerts) of valsartan-containing products manufactured using active pharmaceutical ingredient (API) from Mylan Pharmaceuticals. Mylan voluntarily recalled (/safety/recalls-market-withdrawals-safety-alerts) valsartan-containing products on November 20.

Teva is recalling all lots of amlodipine and valsartan combination tablets and amlodipine, valsartan, and hydrochlorothiazide (HCTZ) combination tablets due to the presence of N-Nitrosodiethylamine (NDEA). Teva has recalled other valsartan-containing products in recent months due to the presence of N-Nitrosodimethylamine (NDMA). With this recall, Teva has now recalled all their unexpired valsartan-containing products from the U.S. market.

The agency continues to investigate and test all angiotensin II receptor blocker (ARBs) for the presence of NDMA and NDEA and is taking swift action when it identifies these impurities that are above acceptable levels.

FDA has updated the list of valsartan products under recall (/media/118231/download) and the list of valsartan products not under recall (/media/118232/download). The agency reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know that not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

11/21/2018: UPDATE - FDA alerts patients and health care professionals to Mylan's recall of valsartan products due to NDEA

Update [11/21/2018] FDA is alerting patients and health care professionals to Mylan Pharmaceuticals' voluntary recall of 15 lots of valsartan-containing products due to the presence of N-Nitrosodiethylamine (NDEA).

Not all Mylan valsartan-containing products distributed in the U.S. are being recalled. Mylan is recalling only those lots of valsartan-containing products that tested positive for NDEA above the acceptable level. The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above acceptable levels.

FDA has updated lists of valsartan products under recall (/media/118231/download)and valsartan products not under recall (/media/118232/download). Additionally, FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

11/9/2018: UPDATE - FDA alerts patients and health care professionals to Sandoz's losartan potassium and hydrochlorothiazide recall of one lot due to NDEA

Update [11/9/2018] FDA is alerting patients and health care professionals to Sandoz's voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/sandoz-inc-issues-voluntary-nationwide-recall-one-lot-losartan-potassium-and-hydrochlorothiazide-due) of one lot – JB8912 – of losartan potassium and hydrochlorothiazide 100mg/25mg tablets, that contain losartan, an angiotensin II receptor blocker (ARB), and hydrochlorothiazide, a diuretic, used in combination for the treatment of hypertension. Sandoz's product was made using an active pharmaceutical ingredient (API) that has tested positive for NDEA. The API was manufactured by Zhejiang Huahai Pharmaceutical Co. Ltd, which is on import alert (https://www.accessdata.fda.gov/cms_ia/importalert_189.html).

Sandoz's losartan drug products make up less than 1 percent of the total losartan drug products in the U.S. market.

FDA continues to investigate the presence of NDEA and NDMA, which are probable human carcinogens, in ARBs and is taking swift action when it identifies unacceptable impurities in API and finished drug products.

FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDEA or NDMA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

10/30/2018: UPDATE - FDA alerts patients and health care professionals to ScieGen's irbesartan recall due to NDEA

Certain irbesartan products labeled as Westminster Pharmaceuticals Inc. and GSMS Inc. recalled

Update [10/30/2018] FDA is alerting patients and health care professionals to ScieGen's voluntary recall of certain lots of irbesartan, an angiotensin II receptor blocker (ARB), because they contain N-Nitrosodiethylamine (NDEA), a known animal and suspected human carcinogen (causes cancer). FDA laboratory testing confirmed NDEA in some lots of ScieGen's irbesartan. ScieGen's irbesartan products are labeled as Westminster Pharmaceuticals and Golden State Medical Supply, Inc. (GSMS). See the list of irbesartan products under recall (/media/117814/download). This is the first non-valsartan drug product the agency has found to contain the NDEA impurity.

ScieGen's recall affects about 1 percent of the irbesartan drug products in the U.S. market.

Additionally, Aurobindo, which manufactures the active pharmaceutical ingredient (API) for ScieGen's irbesartan products, is recalling (/safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-limited-issues-voluntary-recall-irbesartan-drug-substance-due-detection-trace) all unexpired lots of its irbesartan API supplied to the U.S. market with NDEA. FDA and Aurobindo laboratory testing confirmed NDEA in certain lots of their irbesartan API.

FDA reminds patients taking any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. Not all ARBs contain NDEA or N-Nitrosodimethylamine (NDMA), a probable human carcinogen previously found in certain recalled valsartan products, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

To date, ScieGen is the only manufacturer of irbesartan drug products found to contain NDEA. FDA continues to test all ARBs for the presence of impurities and has publicly posted two methods for manufacturers and regulatory agencies around the world to test their ARBs for the unexpected NDMA and NDEA impurities. The combined headspace

method (/media/117843/download) and the combined direct injection method (/media/117807/download) can detect and quantify NDMA and NDEA simultaneously in ARB API and finished drug products.

FDA continues to work with API and drug manufacturers to ensure their products are not at risk for NDMA or NDEA formation. The agency reminds manufacturers they are responsible for developing and using suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects new or higher levels of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients.

For additional information about ARB products, see:

- list of valsartan products under recall (/media/118231/download)
- list of valsartan products not under recall (/media/118232/download)

10/24/2018: UPDATE - FDA updates recalled valsartan-containing product information

Update [10/24/2018] FDA continues to evaluate valsartan-containing products and other angiotensin II receptor blockers (ARBs), and has updated the list of products included in the recall (/media/118231/download) to add one additional lot of RemedyRepack.

10/16/2018: UPDATE - FDA releases additional NDMA/NDEA detection method

Update [10/16/2018] FDA is posting a gas chromatography-tandem mass spectrometry (GC-MS/MS) method (/media/117807/download) utilizing liquid injection for detecting the presence of impurities N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) in valsartan drug products.

This method provides an additional option for regulators and industry to detect NDMA and NDEA impurities. This method can be used alone or in combination with the combined gas chromatography-mass spectrometry (GC/MS) headspace method (/media/117843/download) the agency recently posted. Like the previously posted methods, this method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

10/11/2018: UPDATE - FDA releases method for detection and quantification of both NDMA and NDEA

Update [10/11/2018]] FDA is posting a redeveloped combined gas chromatography-mass spectrometry (GC/MS) headspace (/media/117843/download) method for detecting the presence of impurities N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) in valsartan drug products.

FDA previously posted a GC/MS method for detection of NDMA in valsartan products. Upon detection of NDEA in valsartan products manufactured by Zhejiang Huahai Pharmaceuticals, FDA redeveloped the testing method so that it can be used to detect and quantify levels of both NDMA and NDEA. This method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

FDA is also working on a GC/MS direct injection method for detection of NDMA and NDEA. We will post the method when it is available. This will provide an additional option for regulators and industry to use to detect both impurities.

10/5/2018: UPDATE - FDA posts laboratory analysis of NDMA levels in recalled valsartan products

Update [10/5/2018] FDA posted laboratory test results showing NDMA levels in recalled valsartan products. FDA will also post test results (/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products) and an assessment of the cancer risk from NDEA when they are available.

9/28/2018: UPDATE - FDA places Zhejiang Huahai Pharmaceuticals on import alert

Update [9/28/2018] FDA placed Zhejiang Huahai Pharmaceuticals on import alert (https://www.accessdata.fda.gov/cms_ia/importalert_189.html) on September 28, 2018, to protect U.S. patients while the active pharmaceutical ingredient (API) manufacturer fully determines how impurities were introduced into its API and remediates its quality systems. The import alert stops all API made by ZHP and finished drug products made using ZHP's API from legally entering the United States. FDA's action follows a recent inspection (/media/117875/download) at ZHP's facility.

FDA reminds manufacturers that it is their responsibility to develop and use suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects new or higher levels of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients.

9/24/2018: UPDATE - FDA updates recall lists and releases method for the detection and quantification of NDMA in valsartan

Update [9/24/2018] FDA has updated the list of valsartan products not under recall (/media/118232/download) with five Teva products that were not previously on either list.

9/13/2018: PRESS RELEASE - FDA provides update on its ongoing investigation into valsartan products; and reports on the finding of an additional impurity identified in one firm's already recalled products

Go to Press Release (/news-events/press-announcements/fda-provides-update-its-ongoing-investigation-valsartan-products-and-reports-finding-additional)

8/30/2018: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings

Go to FDA Statement (/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current)

8/24/2018: UPDATE - FDA updates recall lists

Update [8/24/2018] Torrent Pharmaceuticals Limited is expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/updatedadditional-lots-added-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall). FDA has updated the list of valsartan products under recall (/media/118231/download).

8/22/2018: UPDATE - FDA updates recall lists and releases method for the detection and quantification of NDMA in valsartan

Update [8/22/2018] Torrent Pharmaceuticals Limited is expanding its voluntary recall to all lots of unexpired valsartan-containing drug products due to the detection of NDMA in the active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai

Pharmaceuticals.

RemedyRepack, a repackager of Torrent's valsartan/amlodipine/hydrochlorothiazide (HCTZ) tablets, has also recalled.

FDA has updated the list of valsartan products under recall (/media/118231) and the list of valsartan products not under recall (/media/118232/download).

Additionally, FDA is releasing a gas chromatography-mass spectrometry (GC/MS) headspace method (/media/115965/download) for manufacturers and regulators to detect and quantify NDMA in valsartan API and finished drug products. The agency is using this method to test potential NDMA-containing APIs and drug products. This method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

8/20/2018: UPDATE - FDA updates recalled valsartan-containing product information and presents NDMA levels in some foods

Update [8/20/2018] FDA is alerting health care professionals and patients that Torrent Pharmaceuticals Limited is voluntarily recalling (/safety/recalls-market-withdrawals-safety-alerts/torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-valsartan-amlodipine-hctz-tablets) 14 lots of valsartan/amlodipine/hydrochlorothiazide (HCTZ) tablets. Not all Torrent valsartan products distributed in the U.S. are being recalled.

FDA recently learned Torrent used affected valsartan active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai Pharmaceuticals. FDA testing confirmed NDMA in some Torrent products.

To date, Torrent has not received any reports of adverse events related to this recall.

FDA has updated the list of valsartan products under recall (/media/118231) and the list of valsartan products not under recall (/media/118232/download) to incorporate additional repackagers of Camber's valsartan products and Torrent's recall.

NDMA is a known environmental contaminant. For context, it is found in water and foods including meats, dairy products and vegetables.

Estimated Range of Daily NDMA Consumption for certain foods (Recommended daily food consumption rates based on Dietary Guidelines for Americans 2015-2020 (https://health.gov/dietaryguidelines/2015/guidelines/))

- Cured meat - 0.004-0.23 micrograms[1]

- Smoked meat - 0.004-1.02 micrograms[1]
- Grilled meat - 0.006-0.13 micrograms[1]
- Bacon - 0.07-0.09 micrograms[2]
    - In more ordinary terms, for example, one pound of bacon may contain 0.304-0.354 micrograms of NDMA

FDA reminds patients taking valsartan from a recalled lot that they should continue taking their current medicine until their doctor or pharmacist provides a replacement or a different treatment option. Not all valsartan products contain NDMA, so pharmacists may be able to provide a refill of valsartan medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

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[1] *Mavelle, T., B. Bouchikhi, and G. Debry, The occurrence of volatile N-nitrosamines in French foodstuffs. Food Chemistry, 1991. 42(3): p. 321-338.*

[2] *Park, J., et al., Distribution of Seven N-Nitrosamines in Food. Toxicol Res, 2015. 31(3): p. 279-288.*

8/9/2018: UPDATE - FDA updates recalled valsartan-containing product information

Update [8/9/2018] FDA has updated the list of valsartan products under recall (/media/118231) and the list of valsartan products *not* under recall (/media/118232/download) to incorporate recalls of valsartan-containing products manufactured by Hetero Labs Limited, in India, labeled as Camber Pharmaceuticals Inc. Not all Camber valsartan products distributed in the U.S. are being recalled.

Camber Pharmaceuticals is recalling (/safety/recalls-market-withdrawals-safety-alerts/camber-pharmaceuticals-inc-issues-voluntary-nationwide-recall-valsartan-tablets-usp-40mg-80mg-160mg) certain valsartan tablets because they contain the impurity N-nitrosodimethylamine (NDMA) in the active pharmaceutical ingredient (API). Hetero Labs manufactures the API for the Camber products using a process similar to Zhejiang Huahai Pharmaceuticals.

Test results from Hetero Labs show the amount of NDMA found in its valsartan API exceeds acceptable levels; although it is generally lower than the amount discovered in the API manufactured by Zhejiang.

FDA is testing samples of valsartan API and finished products to confirm the extent and amount of NDMA and help inform the ongoing investigation. The agency has also contacted other manufacturers of valsartan API to determine if their manufacturing processes are at risk for the formation of NDMA, and is working with them to ensure NDMA is not present in future valsartan API.

Valsartan is an angiotensin II receptor blocker (ARB), and FDA is investigating whether other types of ARBs are at risk for the presence of NDMA.

Recalled valsartan products labeled as Camber may be repackaged by other companies. FDA will provide updates as more information becomes available.

8/2/2018: UPDATE - FDA updates recalled valsartan-containing product information and reminds API manufacturers to evaluate processes for unsafe impurities

Update [8/2/2018] FDA continues to evaluate valsartan-containing products and has updated the list of products included in the recall (/media/118231/download) and the list of products *not* included in the recall (/media/118232/download). In addition to updating the lists, FDA revised information related to A-S Medication on the list of products included in the recall. The agency will continue to provide information when it becomes available.

FDA is working with drug manufacturers to ensure future valsartan active pharmaceutical ingredients (APIs) are not at risk of NDMA formation. The agency reminds manufacturers to thoroughly evaluate their API manufacturing processes, and changes to those processes, to detect any unsafe impurities. If a manufacturer detects new or higher levels of impurity, they should take action to prevent changes to the product's safety profile.

7/27/2018: UPDATE - FDA updates recalled valsartan-containing product information

Update [7/27/2018] FDA is updating health care professionals and patients after discovering that several additional companies that repackage drug products are also recalling valsartan-containing products.

FDA has product recall information from three additional repackagers of valsartan-containing products made by Teva Pharmaceuticals and Prinston Pharmaceuticals Inc. – labeled as A-S Medication Solutions LLC, AvKARE and RemedyRepack – and the agency has added them to the recalled products list. Two of these companies, A-S Medication and RemedyRepack, may also distribute valsartan products not affected by the recall. The agency is confirming this information and will provide an update once it is available.

The following additional repackagers are recalling or are expected to recall valsartan-containing products. FDA is working to gather product recall information from these companies and has removed them from the list of products that are not impacted by this recall:

- Bryant Ranch Prepack Inc.
- H. J. Harkins Company Inc. *(this company was not originally included on either list)*
- Lake Erie Medical, doing business as Quality Care Products LLC
- NuCare Pharmaceuticals Inc.
- Northwind Pharmaceuticals
- Proficient Rx

It is possible that not all valsartan-containing products repackaged by these companies are impacted by the recall. **FDA continues to evaluate valsartan-containing products** and will update the list of products included in the recall (/media/118231/download) and the list of products *not* included in the recall (/media/118232/download) as more information becomes available.

7/27/2018: UPDATE - Analysis of N-nitrosodimethylamine (NDMA) Levels in Recalled Valsartan in the U.S.

Update [7/27/2018] On July 13th, FDA announced a recall of certain batches of valsartan tablets because of an impurity, a chemical known as N-nitrosodimethylamine (NDMA). Valsartan is a medication commonly used to treat high blood pressure and heart failure.

NDMA has been found to increase the occurrence of cancer in animal studies. These animal studies were done using amounts of NDMA much higher than the impurity levels in recalled valsartan batches. Based on these animal studies, the U.S. Environmental Protection Agency considers NDMA a probable human carcinogen (https://www.epa.gov/sites/production/files/2017-10/documents/ndma_fact_sheet_update_9-15-17_508.pdf)—a chemical that can increase the risk of cancer in humans. NDMA is found in some water supplies and in some foods[1]. Consuming up to 96 nanograms NDMA/day is considered reasonably safe for human ingestion[2]. It is estimated that over the course of a person's lifetime, consuming this amount of NDMA would result in less than one additional case of cancer for every 100,000 people. To put this in context, currently one out of every three people in the US will experience cancer in their lifetime.

The amounts of NDMA found in the recalled batches of valsartan exceeded these acceptable levels. The agency wanted to put some context around the actual potential risk posed to patients who used versions of valsartan that may have contained high levels of NDMA. Based on records from the manufacturer of the recalled valsartan, some levels of the impurity may have been in the valsartan-containing products for as long as four years. FDA scientists estimate that if 8,000 people took the highest valsartan dose (320 mg) from the recalled batches daily for the full four years, there may be one additional case of cancer over the lifetimes of these 8,000 people. This assessment led to FDA's decision to have these batches recalled.

Patients taking valsartan from a recalled batch should continue taking their current medicine until their doctor or pharmacist provides a replacement or a different treatment option. It is important to know that not all valsartan products contained NDMA, so pharmacists may be able to provide a refill of valsartan medication from batches that that are not affected by the recall, or doctors may prescribe a different medication that treats the same indications.

FDA continues to evaluate the safety of valsartan-containing products and will update the list of products included in the recall (/media/118231/download) and the list of products not included in the recall (/media/118232/download) as more information becomes available. If you are taking a valsartan product, be sure to check to back as the lists may change.

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[1] *From Toxnet: https://toxnet.nlm.nih.gov/ (https://toxnet.nlm.nih.gov/)*

Average Daily Intake: *WATER: (assume 3 to 6 ng N-nitrosodimethylamine/l)(1) 6 to 12 ng; direct intake from drinking water is probably much less than 1 ug/day(2). FOOD: (assume <0.1 to="" 84="" ug/kg)(4)=""><0.16 to="" 134="">*
[(1) Kimoto WI et al; Water Res 15: 1099-1106 (1981) (2) USEPA; Ambient Water Quality Criteria Doc: Nitrosamines p.C-14 (1980) EPA 440/5-80-064 (4) IARC; IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 17: 125-76 (1978)]

[2] *The calculated acceptable intake for NDMA is based on methods described in the ICH Guidance M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf*

(http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf))

7/24/2018: UPDATE - FDA publishes a list of valsartan-containing products not part of the recall

Update [7/24/2018] FDA is updating health care professionals and consumers on the agency's progress in responding to the ongoing recalls of valsartan, which is used to treat high blood pressure and heart failure, due to the presence of NDMA. The agency has posted a list of valsartan-containing products not impacted (/media/118232/download) by this recall. **FDA continues to evaluate valsartan-containing products** and will update the list of products included in the recall (/media/118231/download) and the list of products *not* included in the recall (/media/118232/download) as more information becomes available.

Manufacturers of these products often produce multiple dosage strengths, however not all of them are being recalled. FDA recommends health care professionals and patients carefully check these lists. Health care professionals and patients should check this statement frequently for any updates.

FDA reminds consumers to continue taking your current medicine until your doctor or pharmacist gives you a replacement or a different treatment option. Untreated hypertension (high blood pressure) leads to an increase in the risk of heart attacks and stroke. Untreated heart failure increases the risk of hospitalization and death.

Consumers and health care professionals should continue to report any adverse reactions with valsartan-containing products, to the FDA's MedWatch program (/medwatch-fda-safety-information-and-adverse-event-reporting-program) to help the agency better understand the scope of the problem:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home)
- Download and complete the appropriate form, then submit it via fax at 1-800-FDA-0178

7/18/2018: STATEMENT - FDA updates health care professionals and patients on recent valsartan recalls

[7/18/2018] The U.S. Food and Drug Administration is updating health care professionals and consumers following a recent FDA press release (/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity) about voluntary recalls of several drug products containing the active pharmaceutical ingredient (API) valsartan. Valsartan is used to treat high blood pressure and heart failure. Not all products containing valsartan are being recalled, and this update will clarify which valsartan-containing products are being recalled.

The recalled products contain an impurity, N-nitrosodimethylamine (NDMA), in the API manufactured by Zhejiang Huahai Pharmaceuticals, Linhai, China. The presence of the potentially cancer-causing NDMA was unexpected, and the agency believes the NDMA is related to changes in the way the active substance was manufactured. Some levels of the impurity may have been in the valsartan-containing products for as long as four years.

The investigation into valsartan-containing products is ongoing, and the following list may change. We will update this statement as we have more information.

There are currently three voluntary recalls related to the NDMA impurity detected in the valsartan API:

- **Teva Pharmaceuticals USA labeled as Major Pharmaceuticals** — recall is at the **retail level** because these products are only used in facilities where they are directly administered to patients by health care professionals: Valsartan 80 mg and 160 mg products;
- **Prinston Pharmaceuticals Inc. labeled as Solco Healthcare LLC** — recall is at the **consumer/user level**: Valsartan 40 mg, 80 mg, 160 mg, and 320 mg; and valsartan/HCTZ 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, and 320 mg/25 mg products; and
- **Teva Pharmaceuticals labeled as Actavis LLC** — recall is at the **consumer/user level**: Valsartan 40 mg, 80 mg, 160 mg, and 320 mg; and valsartan/HCTZ 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, and 320 mg/25 mg products.

Detailed list of products included in the recall (/media/118231/download) (PDF - 87 KB)

What should patients know:

- Continue taking your current medicine until your doctor or pharmacist gives you a replacement or a different treatment option.
- Not all valsartan-containing medications are affected and being recalled.

- If you are taking any medication containing valsartan, compare the information on your prescription bottle with the information in this list (/about-fda/page-not-found) (company, National Drug Code, lot number) to determine if your current medicine has been recalled. If you are not certain, contact your pharmacist.
- If you have medicine included in the recall, contact your pharmacist. The pharmacist may be able to provide you with valsartan made by another company. If not, contact your doctor immediately to discuss other treatment options.

What health care professionals should know:

- FDA has determined the recalled valsartan products pose an unnecessary risk to patients. Therefore, FDA recommends patients use valsartan-containing medicines made by other companies or consider other available treatment options for the patient's medical condition.
- If you have medication samples from these companies, quarantine the products and do not provide them to patients.

Consumers and health care professionals should report any adverse reactions with valsartan-containing products, to the FDA's MedWatch program (https://www.fda.gov/safety/medwatch/) to help the agency better understand the scope of the problem:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home)
- Download and complete the appropriate form, then submit it via fax at 1-800-FDA-0178

7/13/2018: PRESS RELEASE - FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity

Go to Press Release (/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity)

FDA-published testing methods to provide options for regulators and industry to detect NDMA and NDEA impurities

The links below are to FDA-published testing methods to provide options for regulators and industry to detect nitrosamine impurities in ARB drug substances and drug products. These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

- Combined headspace method (/media/117843/download): a GC/MS method that allows determination of both N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) simultaneously
- Combined direct injection method (/media/117807/download): a GC-MS/MS method that allows for determination of both NDMA and NDEA simultaneously
- Direct injection GC-MS method (/media/123409/download): a method that can detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), and N-nitrosodibutylamine (NDBA)
- Headspace GC-MS method (/media/124025/download): a method that can detect NDMA, NDEA, NDIPA, and NEIPA
- LC-HRMS method (/media/125478/download): a method that can detect NDMA, NDEA, NEIPA, NDIPA, NDBA, and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)
- RapidFire-MS/MS method (/media/125477/download): a method that can detect NEIPA, NDIPA, NDBA, and NMBA. We do not recommend using this method to detect NDMA or NDEA because it is less sensitive to those impurities.

The LC-HRMS and RapidFire-MS/MS methods are the first methods FDA has posted for detecting NMBA. The European Directorate for the Quality of Medicines (EDQM) has also published methods to detect NDMA and NDEA (https://www.edqm.eu/en/ad-hoc-projects-omcl-network) (http://www.fda.gov/about-fda/website-policies/website-disclaimer). FDA has not validated EDQM's methods.

Resources for You

- Search ARBs Recalls List (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and)
- Recalls of ARBs including Valsartan, Losartan and Irbesartan (/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan)

- Nitrosamine Impurities in Medications (/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications)

Exhibit Q

N-Nitrosodimethylamine

CASRN 62-75-9 | DTXSID7021029

- IRIS Summary (PDF) (11 pp, 105 K)

Key IRIS Values | Other EPA Information

Noncancer Assessment

Reference Dose for Oral Exposure (RfD) (PDF) (11 pp, 105 K)
Not assessed under the IRIS Program. Last Updated:

Reference Concentration for Inhalation Exposure (RfC) (PDF) (11 pp, 105 K)
Not assessed under the IRIS Program.

Cancer Assessment

Weight of Evidence for Cancer (PDF) (11 pp, 105 K)
Last Updated: 01/31/1987

WOE Characterization	Framework for WOE Characterization
B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)	Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986)

Basis:

- Induction of tumors at multiple sites in both rodents and nonrodent mammals exposed by various routes.
- This may be a synopsis of the full weight-of-evidence narrative.

Quantitative Estimate of Carcinogenic Risk from Oral Exposure (PDF) (11 pp, 105 K)
Oral Slope Factor: 5.1×10^{1} per mg/kg-day
Drinking Water Unit Risk: 1.4×10^{-3} per µg/L
Extrapolation Method: Weibull, extra risk
Tumor site(s): Hepatic
Tumor type(s): Liver tumors (Peto et al., 1984)

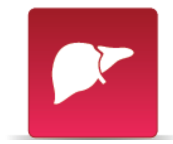
Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure (PDF) (11 pp, 105 K)

Inhalation Unit Risk: 1.4×10^{-2} per µg/m^3
Extrapolation Method: Weibull, extra risk
Tumor site(s): Hepatic
Tumor type(s): Liver tumors (Peto et al., 1984)

Related Links

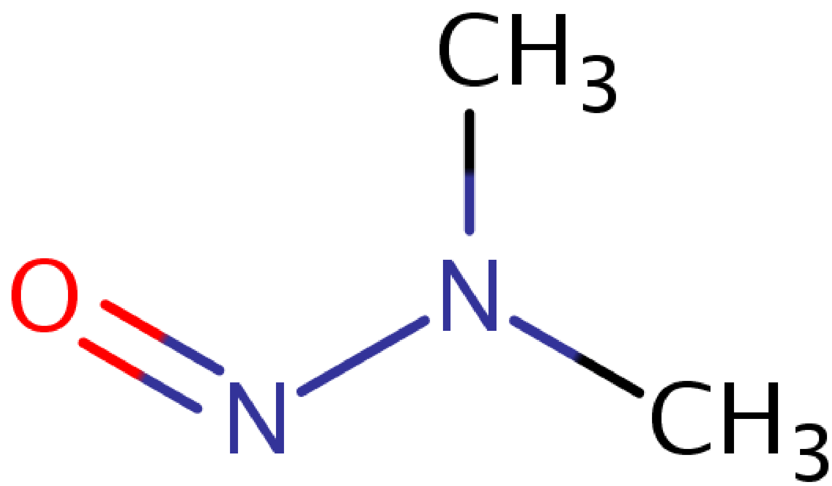
- EPA Chemicals Dashboard - N-Nitrosodimethylamine

Tumor Sites



Hepatic

Chemical Structure for N-Nitrosodimethylamine



Synonyms

- Dimethylamine, n-nitroso
- Dimethylnitrosamin
- Dimethylnitrosamine
- Dmna: dmn
- Methylamine, n-nitrosodi-

more synonyms

LAST UPDATED ON {MONTH DAY, YYYY}

Exhibit R

N-Nitrosodiethylamine

CASRN 55-18-5 | DTXSID2021028

- IRIS Summary (PDF) (11 pp, 106 K)

Key IRIS Values | Other EPA Information

Noncancer Assessment

Reference Dose for Oral Exposure (RfD) (PDF) (11 pp, 106 K)
Not assessed under the IRIS Program. Last Updated:

Reference Concentration for Inhalation Exposure (RfC) (PDF) (11 pp, 106 K)
Not assessed under the IRIS Program.

Cancer Assessment

Weight of Evidence for Cancer (PDF) (11 pp, 106 K)
Last Updated: 01/31/1987

WOE Characterization	**Framework for WOE Characterization**
B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)	Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986)

Basis:

- Induction of tumors at multiple sites in both rodent and nonrodent species exposed by various routes.
- This may be a synopsis of the full weight-of-evidence narrative.

Quantitative Estimate of Carcinogenic Risk from Oral Exposure (PDF) (11 pp, 106 K)
Oral Slope Factor: 1.5×10^{2} per mg/kg-day
Drinking Water Unit Risk: 4.3×10^{-3} per µg/L
Extrapolation Method: Weibull, extra risk
Tumor site(s): Hepatic
Tumor type(s): Liver tumors (Peto et al., 1984)

Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure (PDF) (11 pp, 106 K)

Inhalation Unit Risk: 4.3×10^{-2} per $\mu g/m^3$
Extrapolation Method: Weibull, extra risk
Tumor site(s): Hepatic
Tumor type(s): Liver tumors (Peto et al., 1984)

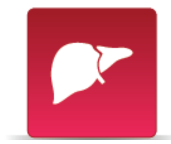
You will need Adobe Reader to view some of the files on this page. See EPA's PDF page to learn more.

Contact Us to ask a question, provide feedback or report a problem.

Related Links

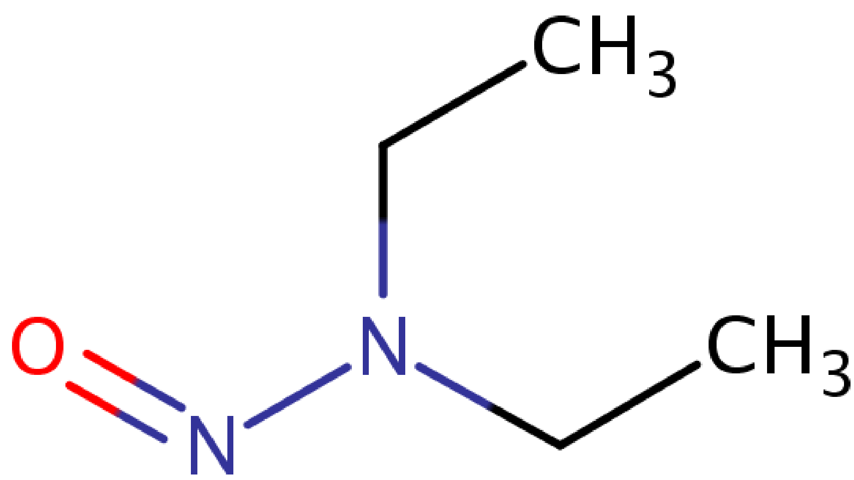
- EPA Chemicals Dashboard - N-Nitrosodiethylamine

Tumor Sites



Hepatic

Chemical Structure for N-Nitrosodiethylamine



Synonyms

- Dana: den
- Dena
- Diaethylnitrosamin
- Diethylamine, n-nitroso
- Diethylnitrosamine

more synonyms

LAST UPDATED ON {MONTH DAY, YYYY}

Exhibit S

Welcome

usp

Empowering a healthy tomorrow

SUMMARY, HIGHLIGHTS and TIMELINE of GENERAL CHAPTER <1469> NITROSAMINE IMPURITIES

By: Edmond Biba
Senior Scientific Liaison,
Science – General Chapters

Webinar
July 28, 2020

Background

Introduction

- Nitrosamines are common chemicals in water and foods including cured and grilled meats, dairy products and vegetables. Everyone is exposed to some level of nitrosamines.
- However, their presence in medicines, even at trace level is considered unacceptable because Nitrosamine impurities are probable human carcinogens.
- They are part of a group of high potency mutagenic carcinogens referred to as the "cohort of concern" in ICH M7. This "cohort of concern comprises aflatoxin-like, N-nitroso- (functional group of nitrosamines), and alkyl-azoxy compounds

Exhibit T

Solco has designated Exhibit T as confidential. Plaintiffs hereby challenge that designation. In accordance with the Court's Confidentiality and Protective order, Plaintiffs will forward the Exhibit to the Court directly via email for its in camera review.